



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification <sup>5</sup> : C07K 5/02, 5/06, 5/08 A61K 37/43, C07D 401/12 C07D 403/12, 209/18, 217/12</p>	<p>A2</p>	<p>(11) International Publication Number: WO 93/20099 (43) International Publication Date: 14 October 1993 (14.10.93)</p>
<p>(21) International Application Number: PCT/GB93/00614 (22) International Filing Date: 25 March 1993 (25.03.93) (30) Priority data: 9206757.8 27 March 1992 (27.03.92) GB (71) Applicants (for all designated States except AT BE CH DE DK ES FR GB GR IE IT LU FERRING B.V. [NL/NL]; Hulswitweg 6, P.O. Box 9578, NL-2003 LN Haarlem (NL). YAMANOUCI PHARMACEUTICAL CO. LTD. [JP/JP]; 3-11, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo 103 (JP). (71)(72) Applicants and Inventors (for AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE RYDER, Hamish [GB/GB]; 79 Dean Road, Bitterne, Southampton, Hampshire SO2 5AQ (GB). KENDRICK, David, Alan [GB/GB]; 258 Southampton Road, Eastleigh, Hampshire SO5 5QU (GB). SEMPLE, Graeme [GB/GB]; 4 Evergreen Close, Marchwood, Southampton, Hampshire SO4 4XU (GB). MIYATA, Keiji [JP/JP]; Pasutoraruraihu 101, 15-5, Azuma 4-chome, Tsukuba-shi, Ibaraki 305 (JP). BATT, Andrzej, Roman [GB/GB]; 41 Kent Road, St. Denys, Southampton, Hampshire SO2 1LJ (GB). MATHEWS, Elizabeth, Alice [GB/GB]; 120 Minster Road, Isle of Sheppey, Kent ME12 3JH (GB). ROOKER, David, Philip [GB/GB]; 7 Aysha Close, Ashington Park, New Milton, Hampshire BH25 5PQ (GB).</p>		<p>NISHIDA, Akito [JP/JP]; 1029-37, Ohaza Kakioka, Yasato-machi, Niihari-gun, Ibaraki 315-01 (JP). AZUZAWA, Shinobu [JP/JP]; 5-9-418, Ninomiya 2-chome, Tsukuba-shi, Ibaraki 305 (JP). SZELKE, Michael [GB/GB]; "Southview", Braishfield, Romsey, Hampshire SO51 0PN (GB). (74) Agent: PHILLIPS &amp; LEIGH; 7 Staple Inn, Holborn, London WC1V 7QF (GB). (81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.</p>
<p>(54) Title: CCK AND/OR GASTRIN RECEPTOR LIGANDS</p> <div data-bbox="438 1218 1331 1659"> </div> <p>(57) Abstract</p> <p>This invention relates to novel compounds with the general structure A-B-C and their pharmaceutically acceptable salts, to medicinal compositions containing them, and to the use of such medicinal compositions in the treatment of certain disease states. The compounds of the invention are represented schematically as A-B-C wherein S<sup>1</sup>-S<sup>4</sup> are in general lipophilic residues, S<sup>5</sup> is a polar or hydrophilic residue, and L<sup>1</sup>-L<sup>5</sup> are optional linking units. The compounds of this invention bind to CCK and/or gastrin receptors with high affinity and are therefore useful in the treatment of diseases which involve the dysfunction of a physiological process regulated by either of these hormones.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LJ	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam
FI	Finland				

## CCK AND/OR GASTRIN RECEPTOR LIGANDS

This invention relates to novel compounds that bind to the CCK and/or gastrin receptor with high affinity, to processes for the preparation of these compounds, and to their use in the treatment of certain disease states.

**BACKGROUND TO THE INVENTION**

Cholecystokinin (CCK) and gastrin are two members of a family of peptide hormones. They were originally discovered and described as agents acting on organs of the gastrointestinal system. CCK stimulates the contraction of the gall bladder and the release of digestive enzymes from the pancreas. Gastrin stimulates the secretion of gastric acid. More recently CCK has been found in the brain, indicating that it may also act as a neurotransmitter or neuromodulator.

Both CCK and gastrin are biosynthesised as prepro-hormones. The biologically active peptides are then released after a series of post-translational modifications. In the case of CCK a number of active forms are produced which vary in the number of amino acid residues they contain. The smallest is a tetrapeptide (CCK-4) and the largest has 58 residues (CCK-58). A variety of gastrins are also known, of which the 17-residue peptide (G-17) is probably one of the most important. Additionally both CCK and gastrin have a tyrosine residue which is found as both the free phenol and as the O-sulphate. All the biologically active forms of both CCK and gastrin share a common tetrapeptide amide sequence at their C-terminus. The C-terminal sequences of the two peptides are:

...-Asp-Tyr<sup>\*</sup>-Met-Gly-T (CCK)

...-Glu-Ala-Tyr<sup>\*</sup>-Gly-T (Gastrin)

(Tyr<sup>\*</sup> = tyrosine residue which is optionally O-sulphated; T = Trp-Met-Asp-Phe-NH<sub>2</sub>)

Apart from its actions on the gall bladder and pancreas mentioned above CCK also influences secretion, absorption and motility in the stomach and intestines, and causes the

secretion of pancreatic hormones such as somatostatin. In the central nervous system CCK appears to be important in anxiogenesis, analgesia and appetite regulation.

Gastrin plays a fundamental part in the control of gastric acid secretion, although the precise mechanism by which this secretion is regulated remains in doubt. Gastrin causes the release of histamine from the ECL-cells in the stomach wall. Histamine then stimulates the parietal cells to secrete acid. It is possible that gastrin can directly stimulate the parietal cells, but this in particular is a point of controversy. Gastrin also increases the blood flow in the stomach wall, but this might also be an indirect effect mediated by histamine, and exerts a trophic effect on the gastric mucosa. (For a more complete review, and leading references, see ref. 1).

CCK and gastrin interact with their target organs through specific receptors located in the cell surface plasma membranes. It is generally agreed that there are two different CCK receptors. The CCK-A (for alimentary) type is found in the peripheral tissue, and is the receptor which mediates the actions of CCK on the pancreas, gall bladder and intestines. It is also found in certain specific brain regions, where it might be involved in the control of appetite. The CCK-B (for brain) receptor type is more widely distributed in the CNS, and is thought to be involved in anxiety and other central actions of CCK. There is only one gastrin receptor type, found particularly in the stomach wall. It appears to show very similar ligand specificity to the CCK-B receptor, and the CCK-B receptor is commonly used as a model for the less readily isolable gastrin receptor.

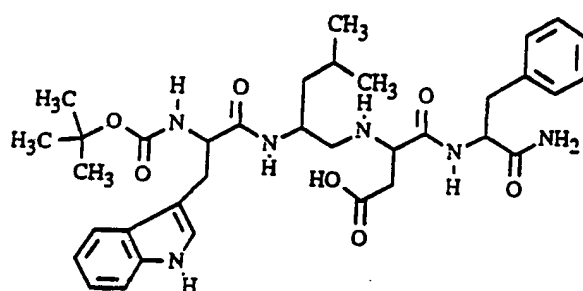
There is evidence that this simple classification system is incomplete. Some tissues appear to have heterogeneous CCK receptor populations, with both high and low affinity sites, and there is some variation in ligand specificity for CCK-A receptors in tissue preparations from different organs. (For more details see ref. 2).

A number of approaches to the discovery of CCK and gastrin receptor agonists and antagonists have been tried and have led to the development of a wide variety of structural types as pharmacological tools for the elucidation of the function of CCK and gastrin *in vivo* and as potential drugs (see Figure).

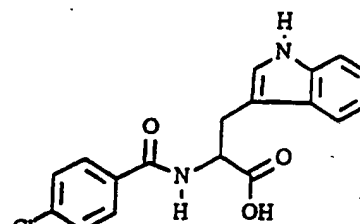
Simple modifications to the natural peptide structures have provided peptides with unusual amino-acids as well as amides, esters and "reduced" and other pseudo-peptides.<sup>3</sup> A group from Abbott Laboratories has shown that conformationally restricted amino-acid surrogates can give compounds of high affinity.<sup>4</sup> Other studies have restricted the peptide conformation by cyclisation between two amino-acid side chains.<sup>5</sup>



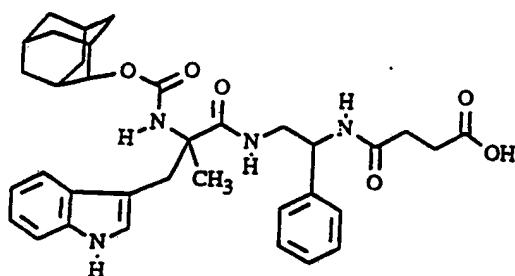
Figure: Some Representative CCK/Gastrin Receptor Ligands



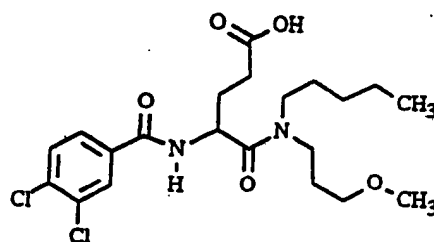
(Martinez *et al*)



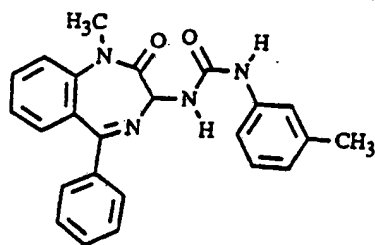
Benzotript



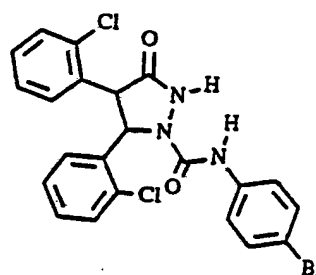
CI-988



Loxiglumide



L-365,260



LY-262691

Tryptophan derivatives have been widely explored. The earliest compounds studied, e.g. benzotript, were not very potent, but more recently disclosed compounds have

demonstrated better affinity.<sup>6</sup> Perhaps the best example of this development is CI-988, a tryptophan "dipeptoid" from Parke-Davis.<sup>7</sup>

A group from Rhone-Poulenc has disclosed a number of compounds which have some analogy with the tryptophan analogues developed by Biomeasure but which lack the indolylmethyl side chain.<sup>8</sup>

Aspartic and glutamic acids have also provided important compounds. Again the original modest lead, proglumide, has been overtaken by more recent developments.<sup>9</sup>

Microbial metabolites are a traditional source of lead structures, and a number of compounds have been shown to have affinity for the CCK-receptor.<sup>10</sup> Probably the most significant of these is asperlicin. It has inspired an enormous effort in the development of benzodiazepine derivatives as CCK ligands. This particular area is probably the most active single area of research into new compounds as CCK and gastrin antagonists.<sup>11</sup>

A group from Lilly has published its findings on a series of quinazolinones which are also inspired by the structure of asperlicin.<sup>12</sup>

A number of groups have disclosed compounds which can be broadly described as small heterocycles with pendant aromatic substituents.<sup>13</sup> These compounds may bind in a similar manner to the benzodiazepines.

Cyclic nucleotide derivatives have been known for some time to be CCK antagonists. The best is dibutyryl cyclic GMP, but its affinity for the receptor is only modest compared with other types of compound.<sup>14</sup>

Finally, it has been demonstrated that some peptides and their analogues, which are not themselves homologous with CCK/gastrin, have some affinity for the CCK receptor. This has been shown in analogues of substance P, calcitonin-gene-related peptide and somatostatin.<sup>15</sup>

#### References.

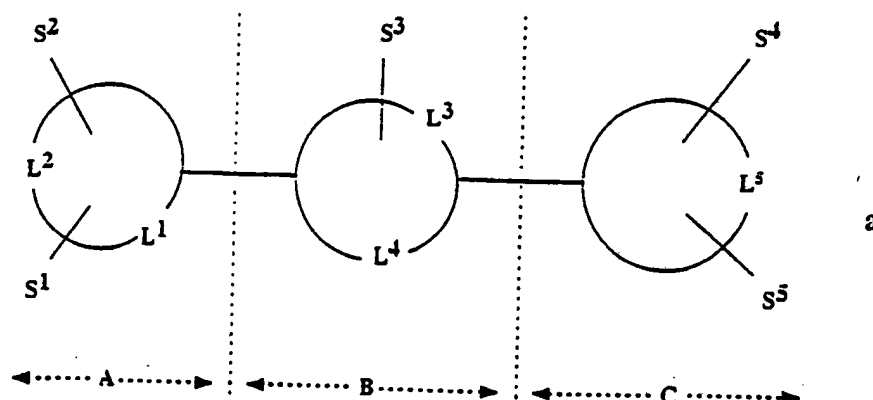
1. J. Martinez, in "Comprehensive Medicinal Chemistry", volume 3, ed. J.C. Emmett, Pergamon Press, Oxford, 1990, pp. 929-943.
2. L.J. Miller, Receptor Purification, 1, 483-495, 1990.

3. K. Shiosaki *et al.*, *J. Med. Chem.*, **33**, 2950-2952, 1990; R. Gonzalez-Muniz *et al.*, *J. Med. Chem.*, **33**, 3199-3204, 1990; M. Boomgaarden *et al.*, *Pharmazie*, **45**, 377-379, 1990; M.F. Lignon *et al.*, *J. Biol. Chem.*, **262**, 7226-7231, 1987; M. Rodriguez *et al.*, *J. Med. Chem.*, **30**, 1366-1373, 1987; C. Mendre *et al.*, *J. Biol. Chem.*, **263**, 10641-10645, 1988; M. Rodriguez *et al.*, *J. Med. Chem.*, **32**, 2331-2339, 1989.
4. K. Shiosaki *et al.*, in "Peptides: Chemistry, Structure and Biology", Proceedings of the 11<sup>th</sup> American Peptide Symposium, ed. J.E. Rivier and G. R. Marshall, ESCOM, Leiden, 1990, pp. 978-980; M.W. Holladay *et al.*, *J. Med. Chem.*, **34**, 455-457, 1991.
5. B. Charpentier *et al.*, *Proc. Natl. Acad. Sci. USA*, **85**, 1968-1972, 1988; M. Rodriguez *et al.*, *Int. J. Peptide Protein Res.*, **35**, 441-451, 1990.
6. R.T. Jensen *et al.*, *Biochimica Biophysica Acta*, **761**, 269-277, 1983; J.F. Kerwin jr. *et al.*, *J. Med. Chem.*, **34**, 3350-3359, 1991; S.H. Kim (for Biomeasure, Inc.), US Patent 4,902,708, 1990.
7. J. Hughes *et al.*, *Proc. Natl. Acad. Sci. USA*, **87**, 6728-6732, 1990; D.C. Horwell *et al.*, *J. Med. Chem.*, **34**, 404-414, 1991.
8. J.D. Bourzat *et al.* (for Rhone-Poulenc Rorer S.A.), International Patent WO 91/12264, 1991; WO 91/13862, 1991.
9. F. Makovec *et al.*, *Eur. J. Med. Chem.*, **21**, 9-20, 1986; R.M. Freidinger *et al.*, *J. Med. Chem.*, **33**, 591-595, 1990; J.F. Kerwin jr. *et al.*, *J. Med. Chem.*, **32**, 739-742, 1989; J.C. Gasc *et al.*, (for Roussel-Uclaf), European Patent Application 0 383 690, 1990; M. Kitazawa *et al.* (for Kissei Pharmaceutical Co. Ltd.), European Patent Application 0 443 064, 1991; F. Makovec *et al.*, *J. Med. Chem.*, **35**, 28-38, 1992.
10. M.G. Bock *et al.*, *J. Med. Chem.*, **29**, 1941-1945, 1986; Y.K.T. Lam *et al.*, *J. Antibiotics*, **44**, 613-625, 1991; D.A. Kendrick *et al.*, *Bioorganic Medicinal Chem Lett.*, **2**, 9-12, 1992.

11. M.G. Bock *et al.*, *J. Med. Chem.*, **32**, 13-16, 1989; Y. Sato *et al.* (for Fujisawa Pharmaceutical Co. Ltd.), European Patent Application 0 360 079, 1990; J.C. Gasc and D. Humbert (for Roussel-Uclaf), European Patent Application 0 376 849, 1990; A.P. Calvet *et al.* (for Jouveinal S.A.), European Patent Application 0 420 716, 1991; M.G. Bock *et al.* (for Merck & Co. Inc.), European Patent Application 0 434 360, 1991; S. Rault *et al.* (for Adir & Co.), European Patent Application 0 446 133, 1991.
12. M.J. Yu *et al.*, *J. Med. Chem.*, **34**, 1505-1508, 1991.
13. M. Honaga *et al.*, *Japan. J. Pharmacol.*, **46**, 319-324, 1988; J.D. Bourzat *et al.* (for Rhone-Poulenc Sante), European Patent Application 0 367 678, 1990; J.P. Bras *et al.* (for Sanofi), European Patent Application 0 432 040, 1991; J.J. Howbert, Presentation at SDR Symposium, "Non-peptide Antagonists for Peptide Receptors", London 1991.
14. J.D. Gardner and R.T. Jensen, *Am. J. Physiol.*, **246**, G471-G476, 1984.
15. L. Zhang, *et al.*, *Biochimica Biophysica Acta*, **972**, 37-44, 1988; P.N. Maton *et al.*, *Peptides*, **11**, 1163-1167, 1990; N. Tahiri-Jouti, *Neuropeptides*, **19**, 65-71, 1991.

## DESCRIPTION OF THE INVENTION

The compounds of the present invention are ligands with a high affinity for CCK and/or gastrin receptors. They can be represented by the general formula A-B-C in which A, B and C are subunits as defined below and are linked by covalent bonds. It is presumed that the compounds of this invention achieve their potency by mimicking the C-terminal tetrapeptide which is common to CCK and gastrin, but this is not necessarily always the case. The important features of A, B and C are represented schematically below as general structure a:



in which:

S<sup>1</sup> is an optional substituent group, but when present is a hydrophobic residue

S<sup>2</sup> is a mandatory substituent, and is always an aromatic (including heteroaromatic) residue

S<sup>3</sup> is also mandatory, and is generally a hydrophobic residue (but with the exceptions mentioned below)

S<sup>4</sup> is mandatory, and is a hydrophobic residue

S<sup>5</sup> is optional, and is generally a hydrophilic or polar residue

L<sup>1</sup> - L<sup>5</sup> are linking elements (covalent bonds or chains of atoms) which are optional with the proviso that if S<sup>1</sup> is present then L<sup>2</sup> must be present, and that at least one of L<sup>3</sup> and L<sup>4</sup> must be present.

Exceptions to the above fall into two categories:

when S<sup>5</sup> is absent S<sup>3</sup> can be a hydrophilic residue, and

when B is a group such as a proline residue then L<sup>3</sup> can take the place of S<sup>3</sup>.

It is not the inventors' intention that the above be regarded as a definition of the invention. It is intended to be an aid to understanding the key features of the compounds of the invention, and it will be used below as a guide in explaining the development of the preferred embodiments of the invention. The precise scope of the invention is defined in Claim 1 below.

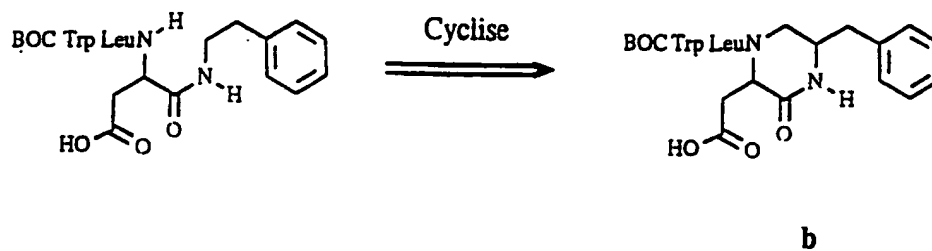
In general, then, A is a unit that can have either one or two hydrophobic residues attached. When only one is present then it is an aromatic system, and A is a group such as (substituted)phenyl carbamoyl, indoleacetyl or isoquinolinecarbonyl. When both hydrophobic residues are present and the linking unit  $L^1$  is absent then A mimics a blocked aromatic amino-acid such as BOC-tryptophan or benzoyl-phenylglycine. When  $L^1$  is present then A is cyclic. The aromatic residue can either be pendant to this ring or fused to it, giving, for example, a phenylproline and an indoline respectively. In these cases  $S^1$  can be absent or it can be any hydrophobic group, for example a BOC- or a benzoyl group.

For subunit B there are three possibilities. When  $L^3$  is present and  $L^4$  is absent then B is analogous to an amino-acid, or a residue that can mimic an amino-acid, such as, for example O-benzyl-threonine or its "reduced" isostere. When  $L^3$  is absent and  $L^4$  is present then B can be considered to be an N-alkyl amino-acid analogue. When both  $L^3$  and  $L^4$  are present then B is cyclic. The ring can in itself constitute the hydrophobic residue  $S^3$ , for example when B is a proline residue. Alternatively, the residue can be a pendant group or, if it is cyclic, it can be fused to the ring of B, giving for example a substituted proline or an indoline respectively.

For subunit C, if  $L^5$  is absent then the subunit is analogous to an N-alkylated amino-acid (as was B with  $L^3$  absent and  $L^4$  present). In this case  $S^5$  must be present, and mimics the backbone of the amino-acid. In some of the embodiments of the invention  $S^5$  is extended and mimics a dipeptide chain. When  $L^5$  is present  $S^5$  can be absent, or if it is present it performs a function analogous to that just described. With  $L^5$  present  $S^4$  can either be pendant to the ring so formed, or it can be fused with it.

We have found that certain combinations of the above options lead to compounds with high affinity for the target receptors, and in some cases with high selectivity between receptor sub-types. The result of our studies is a group of novel compounds with pharmacological properties as good as, and often better than, CCK and gastrin receptor ligands previously described, which makes them useful in the treatment of certain ailments. These compounds are the basis of the present invention.

Conceptually, the compounds of the present invention are derived from the amino-acid sequence of the naturally occurring hormones. The starting point of our investigation was an amide described by Martinez *et al.* (*Int. J. Peptide Protein Res.*, 28, 529-535, 1986). We found that constraining the conformational freedom of the ester by cyclization gave compounds which retained some affinity for both CCK-A and CCK-B receptors. This key step is represented below.



Comparing the structure of the cyclised compound (b) with the diagrammatic representation of the compounds of this invention (a) described above shows the following set of correspondences:

$S^1 = \text{BOC}$

$S^2 = \text{Trp side chain}$

$S^3 = \text{Leu side chain}$

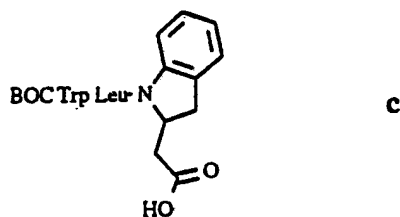
$S^4 = \text{benzyl group}$

$S^5 = \text{carboxymethyl group}$

$L^1 \text{ \& } L^4 \text{ absent}$

$L^2, L^3 \text{ \& } L^5 \text{ present.}$

Further investigation demonstrated that potency was improved, particularly with respect to the CCK-A receptor, if the aromatic residue in  $S^4$  was fused to the C ring (compound c), and that the BOC-amino group could be omitted.



This leads to a first preferred embodiment of the present invention, defined precisely in Claims 19-20, in which:

A is a fused heteroaromatic substituted acyl residue, or an N<sup>α</sup>-blocked tryptophan residue;

B is a hydrophobic amino-acid residue, or a surrogate of one;

C is a benzo-fused piperidine or pyrrolidine, further substituted with a carboxyl or carboxyalkyl residue, which can be blocked as an ester, or extended, for example, by acylating an amino-acid residue.

In particular, this preferred embodiment of the invention includes:

Ethyl (2R)-1-{(*tert*-butyloxycarbonyl-tryptophanyl-leucyl)}-2,3-dihydroindole-2-acetate

Ethyl (2S)-1-{(2S)-2-((*tert*-butyloxycarbonyl-tryptophanyl-amino)-hexanoyl)}-2,3-dihydroindole-2-carboxylate

(2R)-1-{Indole-2-carbonyl-phenylalanyl}-2,3-dihydroindole-2-acetic acid

(2R)-1-{(2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid

3-{(2R)-1-{(2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-yl}-propanoic acid

(2R)-1-{(2S)-2-(5-Fluoroindole-2-carboxylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid

(2R)-1-{(2S)-2-(5-Chloroindole-2-carboxylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid

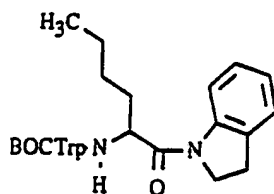
(3R)-2-{(2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

N-{(2S)-1-{(2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetyl}-glycine

3-{(2S)-1-{(2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-carboxylamino}-propanoic acid.

Further investigation revealed that deletion of the S<sup>5</sup> substituent in the compounds typified by c generally resulted in compounds which were more potent and selective for the CCK-A receptor (e.g. compound d).





d

This leads to a second preferred embodiment of the present invention, defined precisely in Claims 16-18, in which:

A is a fused heteroaromatic substituted acyl residue, or an N $\alpha$ -blocked tryptophan residue;

B is usually a hydrophobic amino-acid residue, or a similar surrogate, but may also be a hydrophilic amino-acid residue, or a similar surrogate;

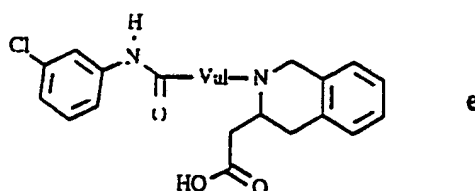
C is a benzo-fused piperidine or pyrrolidine.

In particular, this preferred embodiment of the invention includes;

- 1-{*tert*-Butyloxycarbonyl-tryptophanyl-leucyl}-2,3-dihydroindole
- 1-((2*S*)-2-(*tert*-Butyloxycarbonyl-tryptophanyl-amino)-hexanoyl)-2,3-dihydroindole
- 1-((2*S*)-2-(3-Indole-3-propanoylamino)-hexanoyl)-2,3-dihydroindole
- 1-{*tert*-Butyloxycarbonyl-tryptophanyl-phenylalanyl}-2,3-dihydroindole
- 1-((2*S*)-2-(*tert*-Butyloxycarbonyl-tryptophanyl-amino)-4-phenylbutanoyl)-2,3-dihydroindole
- 1-{*tert*-Butyloxycarbonyl-tryptophanyl-( $\beta$ -O-benzyl)-D-aspartyl}-2,3-dihydroindole
- 1-{*tert*-Butyloxycarbonyl-tryptophanyl-aspartyl}-2,3-dihydroindole
- 1-{*tert*-Butyloxycarbonyl-tryptophanyl-( $\gamma$ -O-benzyl)-glutamyl}-2,3-dihydroindole
- 1-{*tert*-Butyloxycarbonyl-tryptophanyl-glutamyl}-2,3-dihydroindole
- 2-{*tert*-Butyloxycarbonyl-tryptophanyl-D-phenylalanyl}-1,2,3,4-tetrahydroisoquinoline
- 2-((2*R*)-2-(*tert*-Butyloxycarbonyl-tryptophanyl-amino)-4-phenylbutanoyl)-1,2,3,4-tetrahydroisoquinoline.

Modifications at the A subunit of compounds typified by structure c indicated that smaller groups could be employed without incurring a loss of activity. In particular, the replacement of BOC-Trp with an arylcarbamoyl residue (as in compound e) resulted in compounds which had high affinity for the CCK-A and/or CCK-B/gastrin receptor subtypes.

12



This leads to a third preferred embodiment of the present invention, defined precisely in Claims 2-7, in which:

A is a substituted or unsubstituted phenylcarbamoyl residue (i.e. L<sup>1</sup>, L<sup>2</sup> and S<sup>1</sup> are absent);

B is a hydrophobic amino-acid, or a similar surrogate;

C is a piperidine or pyrrolidine which may be benzo-fused or may have a pendant hydrophobic substituent, and which is further substituted with a carboxylor carboxyalkyl sidechain or a derivative thereof.

In particular, this embodiment of the invention includes:

(3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Methylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Acetylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Isopropoxyphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Cyanophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-*tert*-butyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzoyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-(4-chlorobenzyl)-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

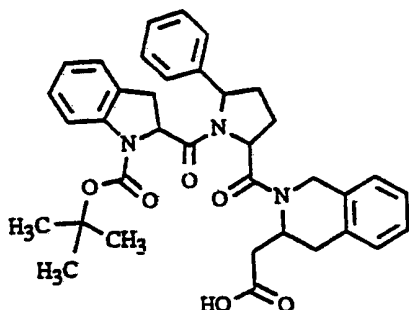
(3R)-2-[(2S)-2-(3-Trifluoromethylphenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

- (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(2S)-2-(N-(3-Chlorophenylcarbamoyl)-methylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(2S)-2-(3,4-Dichlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(2S)-2-(2-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(2S)-2-(4-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(2S)-2-(3-Methoxyphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[N-(3-Chlorophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[N-(3-Bromophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[N-(3-Methylphenylcarbamoyl)-isoleucyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-3,3-dimethylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(S)- $\alpha$ -(3-Chlorophenylcarbamoylamino)-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(S)- $\alpha$ -(3-Methylphenylcarbamoylamino)-cyclohexaneacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(2S)-3-(2-Adamantyloxycarbonylamino)-2-(phenylcarbamoylamino)-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(2S,3R)-2-(3-Chlorophenylcarbamoylamino)-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (2R,4S)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-carboxylic acid
- (2R,4R)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-acetic acid

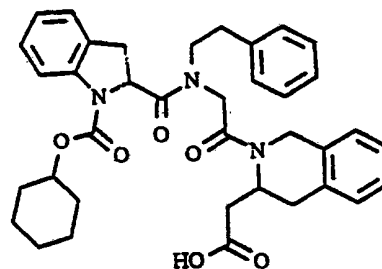
(2R,5S)-1-[N-(3-Chlorophenylcarbamoyl)-(S)-benzyl-threonyl]-5-phenylpyrrolidine-2-carboxylic acid

(3R)-2-[(2S,3R)-3-Benzoyloxy-2-(3-chlorophenylcarbamoylamino)-butyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

The modification of the above structural types to give compounds with consistently high affinity and selectivity for CCK-B/gastrin receptors was more involved, but could be achieved in two ways. The first originated in the discovery that by constraining the conformational freedom of the A subunit with the introduction of L<sup>1</sup> the selectivity for CCK-B receptors was improved. This gain could be further improved by the introduction of L<sup>4</sup> to constrain the B subunit (as in compound f). The affinity and selectivity of these compounds was found to be maintained when L<sup>3</sup> was removed (as in compound g).



f



g

This leads to a fourth preferred embodiment of the present invention, defined precisely in Claims 12-15, in which:

A is a benzo-fused nitrogen heterocyclic acyl residue in which the nitrogen is substituted with a hydrophobic group (i.e. S<sup>1</sup>, S<sup>2</sup>, L<sup>1</sup> and L<sup>2</sup> all present);

B is a hydrophobic amino-acid residue or a similar surrogate, which preferably incorporates some degree of conformational restriction either through cyclization (as in f or by having a 3-amino-2-naphthoyl residue for B) or through N-substitution (as in g);

C is a benzo-fused piperidine or pyrrolidine which may optionally be substituted at up to three positions. If such substituents are present then at least one is hydrophilic (for example a carboxyl or carboxyalkyl).

In particular, this embodiment of the invention includes:

(3R)-2-{N-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-O-benzyl-threonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

- (3R)-2-((2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-4-phenylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (2R)-1-((2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetic acid
- (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-(((2R)-1-*tert*-Butylacetyl-2,3-dihydroindole-2-carboxyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-isoleucyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-((S)- $\alpha$ -((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-phenylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-D-prolyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-((2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-2,3-dihydroindole-2-carboxyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-((2R,3S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-3-phenyl-pyrrolidine-2-carboxyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-((2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-4-phenylthio-pyrrolidine-2-carboxyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (3R)-2-((2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-4-phenylthio-pyrrolidine-2-carboxyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-((2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-4-phenylthio-pyrrolidine-2-carboxyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (3R)-2-((2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-4-benzyloxy-pyrrolidine-2-carboxyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (3R)-2-((2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-4-phenoxy-pyrrolidine-2-carboxyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (3R)-2-((2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-4-phenyl-pyrrolidine-2-carboxyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-((2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-4-phenyl-pyrrolidine-2-carboxyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-((2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-4-benzyl-pyrrolidine-2-carboxyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline

Methyl (3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

(3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

N-[(3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carbonyl]-glycine

(3R)-2-[(2R,5S)-1-[(2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-[(2R,5S)-1-[(2R)-1-Isopropyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-[(2R,5S)-1-[(2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-[(2R,5S)-1-[(2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

(3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butylcarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butylacetyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

N-[(3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetyl]-proline

N-[(3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetyl]-D-proline

(3R)-2-[(2R,5S)-1-[(2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2R,5S)-1-[(2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2R,5S)-1-[(2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydro-benz[f]isoquinoline-3-carboxylic acid

(3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetic acid  
(3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-(N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-(N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-(N-Benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-(N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-(N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.  
(3R)-2-(3-(N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino)-propanoyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-(N-Phenethyl-N-((2R)-1-benzyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-(N-Phenethyl-N-((2R)-1-neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-(N-Phenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-(N-3-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-(N-(2-Oxo-2-phenylethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-(N-(2-(3-Indolyl)ethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-(N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid

(3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[f]isoquinoline-3-acetic acid

(3R)-2-{N-Pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-2,5-dihydropyrrole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-methyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-acetylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxyl}-proline

N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxyl}-proline

N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxyl}-D-proline

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{N-2-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-4-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-2-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-3-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-4-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[h]isoquinoline-3-carboxylic acid

(4RS)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-4-acetic acid

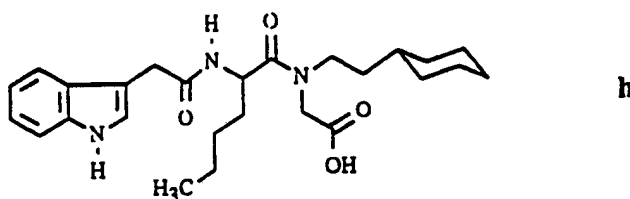


(4R,5S)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-4-acetic acid  
(3R)-2-((2R,5S)-1-((2R)-1-Cyclobutyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-((2R,5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-((2R,5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-((2R,5S)-1-((2R)-1-(2-*exo*-Norbornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-((2R,5S)-1-((2R)-1-Cyclododecyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-(N-Phenethyl-N-((2R)-1-*n*-propyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
N-((3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetyl)-proline  
(3R)-2-(N-2-(2-Methoxyphenyl)ethyl-N-((2R)-1-(*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-((2R,5S)-1-((2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-((2R,5S)-1-((2R)-1-Cycloheptyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-((2R,5S)-1-((2R)-1-((1S)-*endo*-Bornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-((2R,5S)-1-((2R)-1-((1R,2R,3R,5S)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-((2R,5S)-1-((2R)-1-((1S,2S,3S,5R)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid  
(3R)-2-((2R,5S)-1-((2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid  
(3R)-2-((2R,5S)-1-((2R)-1-(1-Piperidino)carbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

- (3R)-2-[(2R,5S)-1-[(2R)-1-(N-Cyclohexyl-N-methylcarbamoyl)-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (3R)-2-[(2R,5S)-1-[(2R)-1-(4-*tert*-Butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (3R)-2-[(2R,5S)-1-[(2R)-1-(2-*cis*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (3R)-2-[(2R,5S)-1-[(2R)-1-(2-*trans*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (3R)-2-[N-Phenethyl-N-[(2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(2R,5S)-1-[(2R)-1-Cyclohexylmethyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- (3R)-2-[(2R,5S)-1-[(2R)-1-(2-Cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
- N-[(3R)-2-[(2R,5S)-1-[(2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carbonyl]-proline
- N-[(3R)-2-[(2R,5S)-1-[(2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carbonyl]-proline
- (3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-propanoic acid
- (3R)-2-[N-3-Methylphenethyl-N-[(2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-[(2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[N-(2-Thienyl)ethyl-N-[(2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[N-[(2RS)-1,2,3,4-Tetrahydronaphth-2-yl]-N-[(2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
- (3R)-2-[(2R,5S)-1-[(2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-(4-methoxyphenyl)-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-[N-(Indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

The second modification which yields potent and selective CCK-B/gastrin receptor ligands involves the deletion of L<sup>5</sup> (equivalent to the excision of the cyclic amide bond from b) to give a series of tertiary amides. In this series S<sup>1</sup> is not required and the compounds are structurally less complex (as in h).



This leads to a fifth preferred embodiment of the present invention, defined precisely in Claims 8-11, in which:

A is an acyl residue with an aromatic substituent;

B is a hydrophobic amino-acid or a similar surrogate;

C is an N-substituted amino-acid or similar surrogate, where the N-substituent is an alkyl, cycloalkyl, aralkyl or aryl group, and the carboxy terminus may be the free acid or may be blocked as an ester or amide, or may be extended, for example, by acylating another amino-acid residue.

In particular, this preferred embodiment of the invention includes:

Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycinate

N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycine

1-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-pyrrolidine

Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-prolinate

N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-proline

N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-pipecolic acid

N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-glycine

1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-pyrrolidine

1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-proline

1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-proline  
1-{N-(Cyclooctylmethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-proline  
1-{3-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-amino}-propanoyl}-pyrrolidine  
N-(3-Cyclohexylpropyl)-N-((2S)-2-(2-indolecarbonylamino)-hexanoyl)-glycine  
N-(3-Cyclohexylpropyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycine  
N-(2-Cyclohexylethyl)-N-((2S)-2-(3-isoquinolinecarbonylamino)-4-phenylbutanoyl)-glycine  
N-{N-Phenethyl-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-proline.  
1-{N-(2-Cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycyl}-D-proline  
1-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-4-phenylbutanoyl)-glycyl}-D-proline

Where the compounds of the present invention are capable of forming salts with inorganic and organic acids and/or bases then those pharmaceutically acceptable salts are included within the scope of the invention. Examples of such salts include sodium, potassium and tetra-alkyl ammonium salts of acidic compounds, and chlorides, sulphates and acetates of basic compounds.

Where the compounds of the present invention contain a carboxylic acid moiety then these may be administered in pro-drug form as simple esters.

## SYNTHETIC METHODS

### GENERAL

The synthesis of the compounds of the present invention can be considered as involving two stages. In Stage 1 the individual components A, B and C in general formula I are prepared from commercially available starting materials if they are not themselves available. During Stage 1 protecting groups may be introduced into A, B and C in order to obviate side reactions in Stage 2. The second phase involves assembling the individual components into the finished compound. During Stage 2, apart from the crucial A-B and B-C bond forming reactions, selective manipulation of the protecting groups may be necessary. At the end of Stage 2 final adjustments can be made to complete the synthesis.

Using general formula I as the target, a typical synthesis might involve the following steps:

**Stage 1**

*pre-A*  $\Rightarrow$  steps  $\Rightarrow$  PG<sup>1</sup>-A

*pre-B*  $\Rightarrow$  steps  $\Rightarrow$  PG<sup>2</sup>-B

*pre-C*  $\Rightarrow$  steps  $\Rightarrow$  C-PG<sup>3</sup>

where PG<sup>1</sup> - PG<sup>3</sup> are protecting groups.

*pre-A* - *pre-C* are commercially available precursors.

**Stage 2**

PG<sup>2</sup>-B + C-PG<sup>3</sup>  $\Rightarrow$  PG<sup>2</sup>-B-C-PG<sup>3</sup>

PG<sup>2</sup>-B-C-PG<sup>3</sup>  $\Rightarrow$  B-C-PG<sup>3</sup>

PG<sup>1</sup>-A + B-C-PG<sup>3</sup>  $\Rightarrow$  PG<sup>1</sup>-A-B-C-PG<sup>3</sup>

PG<sup>1</sup>-A-B-C-PG<sup>3</sup>  $\Rightarrow$  A-B-C

Depending on the precise nature of A, B and C the order in which the components are coupled together may be varied. Thus it might be advantageous to form the A-B fragment first and couple this to C. Another variation is possible when C can be divided into two sub-fragments (e.g. when C is XIX, or XVI with R<sup>14</sup> is XXII). In these cases one of the sub-fragments can be introduced at a late stage. If C is composed of the sub-fragments C<sup>1</sup>-D then Stage 2 of the overall synthesis might be:

PG<sup>2</sup>-B + C<sup>1</sup>-PG<sup>3</sup>  $\Rightarrow$  PG<sup>2</sup>-B-C<sup>1</sup>-PG<sup>3</sup>

PG<sup>2</sup>-B-C<sup>1</sup>-PG<sup>3</sup>  $\Rightarrow$  B-C<sup>1</sup>-PG<sup>3</sup>

PG<sup>1</sup>-A + B-C<sup>1</sup>-PG<sup>3</sup>  $\Rightarrow$  PG<sup>1</sup>-A-B-C<sup>1</sup>-PG<sup>3</sup>

PG<sup>1</sup>-A-B-C<sup>1</sup>-PG<sup>3</sup>  $\Rightarrow$  PG<sup>1</sup>-A-B-C<sup>1</sup>

PG<sup>1</sup>-A-B-C<sup>1</sup> + D  $\Rightarrow$  PG<sup>1</sup>-A-B-C

PG<sup>1</sup>-A-B-C  $\Rightarrow$  A-B-C

The chemistry involved in preparing the compounds of the present invention depends on the nature of A, B and C. The specific Examples which follow make use of reactions which are established in the literature for analogous transformations. It is not the inventors' intention to restrict the scope of this patent solely to those reactions described explicitly in the Examples, but to include other methods which a person competent in the art might employ to achieve the same overall transformation. Also included are such

variations in the protecting groups and the order of assembly of the fragments as might be used by such a competent person.

The general concepts outlined above (preparation of the fragments, coupling, and protecting group manipulation) will now be illustrated more fully in the following non-limiting Examples.

## EXPLANATORY NOTES

In the following Examples:

**R<sub>f</sub>:** TLC was performed on commercial silica plates (Merck Art. 5714)

**HPLC:** Buffer I 0.1% TFA/H<sub>2</sub>O; Buffer II 0.1% TFA/MeCN

System A: Novapak C<sub>18</sub>, 4  $\mu$ , 8x100 mm: linear gradient 40% to 90% II into I over 25 min. at 1.5 mL/min.

System B: Spherisorb C<sub>18</sub>, 5  $\mu$ , 4.6x100 mm: linear gradient 40% to 90% II into I over 25 min. at 0.8 mL/min.

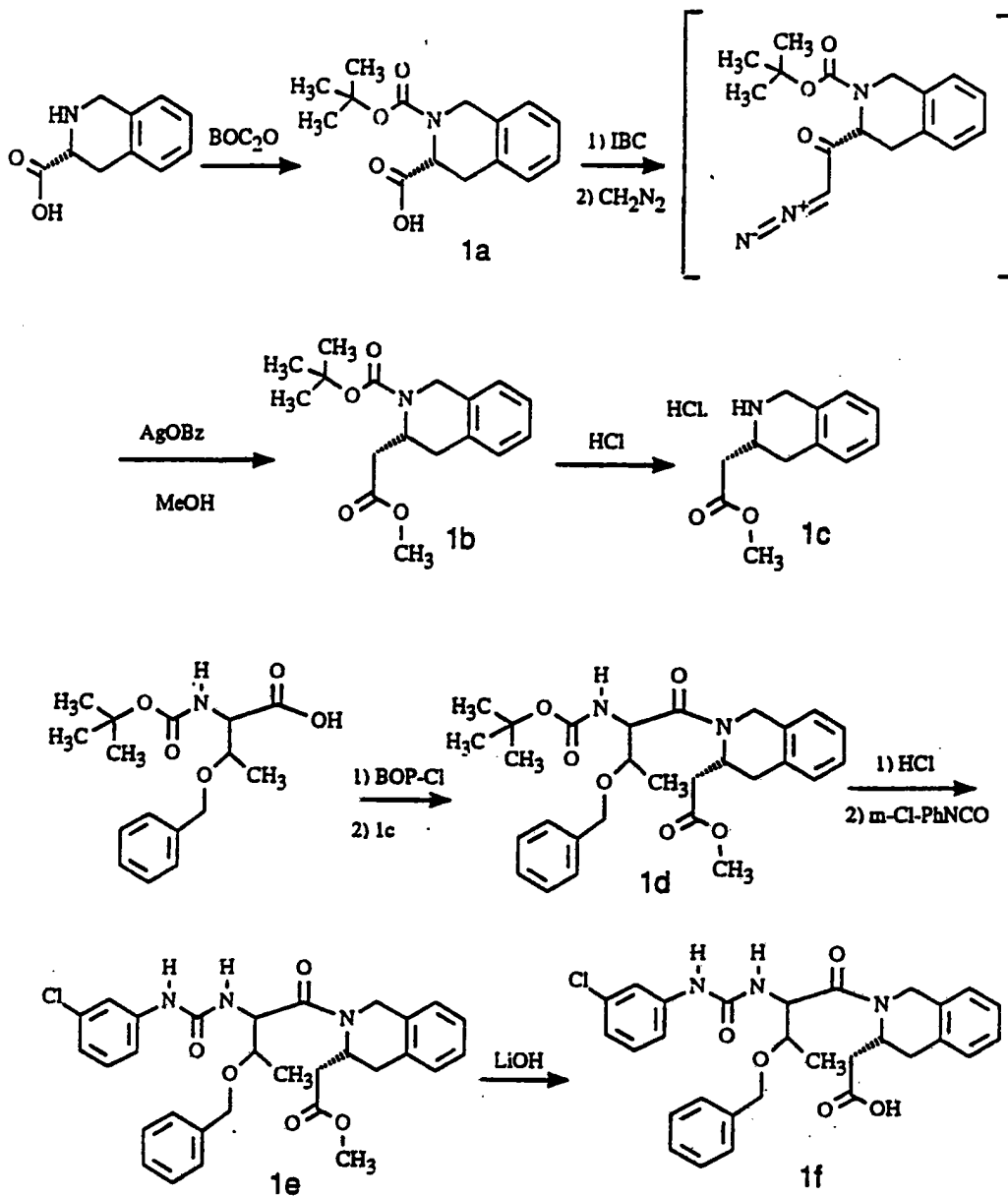
**AAA:** Hydrolysis 6N HCl + phenol at 150°C for 1.5 hr.

**<sup>1</sup>H NMR:** Determined at 270 MHz in CDCl<sub>3</sub>.

**Mass spec:** Positive ion FAB.

Reagents were generally used as supplied without purification. Solvents were HPLC grade, except THF which was distilled from Na/benzophenone. Silica gel for flash chromatography was Merck Kieselgel 60 (230-400 mesh).

## EXAMPLE 1

**1a (3R)-2-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

To a stirred suspension of D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (2.5 g, 14.1 mmol) in dioxan (200 mL) was added di-*tert*-butyl pyrocarbonate (3.66 g, 16.9 mmol) and a solution of KOH (0.79 g, 14.1 mmol) in  $\text{H}_2\text{O}$  (50 mL). The mixture was stirred at room temperature for 5 hr., and then the solvent was evaporated *in vacuo*. The residue was taken up in  $\text{H}_2\text{O}$  and the solution was acidified with 10% aq.  $\text{KHSO}_4$  to pH=2. The mixture was extracted twice with EtOAc, and the combined extracts were

washed with brine, filtered (Whatman<sup>®</sup> 1 PS phase separator), and concentrated *in vacuo*. The residue was triturated with pet. ether (b.p. 60-80°C) to give the title compound as a white solid (3.2 g, 82%).

**1b Methyl (3R)-2-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

To a stirred solution of 1a (10.9 g, 39.5 mmol) in EtOAc (120 mL) was added N-methylmorpholine (4.4 mL, 40 mmol). The solution was cooled to -20°C, and isobutyl chloroformate (5.2 mL, 44 mmol) was added dropwise. The mixture was stirred at -15°C for 20 min., then poured into a solution of diazomethane (from Diazald<sup>®</sup>, 43 g, 200 mmol) in Et<sub>2</sub>O, and the resulting solution was stirred at room temperature for 1 hr. Excess diazomethane was destroyed by the addition of glacial AcOH. The solution was washed successively with 1.0M NaHCO<sub>3</sub>, H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet ether 25:75 v/v) to give (3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinolyl diazomethyl ketone (8.0 g, 26.6 mmol, 67%).

This ketone was dissolved in MeOH (200 mL) and to this solution was added a solution of silver benzoate (2 g, 8 mmol) in Et<sub>3</sub>N. The mixture was stirred at room temperature for 40 min., and then the solvent was evaporated *in vacuo*. The residue was taken up in EtOAc and washed successively with 1.0M NaHCO<sub>3</sub>, H<sub>2</sub>O, brine, 0.3M KHSO<sub>4</sub>, H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 18:82 v/v) to give the title ester (6.5 g, 80%).

**1c Methyl (3R)-1,2,3,4-tetrahydroisoquinoline-3-acetate hydrochloride.**

The BOC-protected ester 1b (6.5 g, 21.3 mmol) was taken up in 4N HCl in dioxan (100 mL) and the solution was stirred at room temperature for 90 min. The solvent was removed *in vacuo*, finally with toluene azeotrope, to give the title compound (5.0 g, 99%).

**1d Methyl (3R)-2-[N-*tert*-butyloxycarbonyl-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

To a stirred solution of BOC-(O-benzyl)-threonine (866 mg, 2.8 mmol) and diisopropylethylamine (0.50 mL, 2.88 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL), cooled to -20°C, was added *bis*(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl, 733 mg, 2.88 mmol). The mixture was stirred at -20°C for 20 min., then 1c (483 mg, 2 mmol) and diisopropylethylamine (0.35 mL, 2 mmol) were added. The mixture was stirred at room temperature overnight, then poured into EtOAc. The solution was washed successively



with 10% KHSO<sub>4</sub>, satd. KHCO<sub>3</sub>, H<sub>2</sub>O and brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v) to give the title compound (678 mg, 68%).

**1e Methyl (3R)-2-[N-(3-chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

A solution of the BOC-protected ester 1d (159 mg, 0.32 mmol) in 4*N* HCl in dioxan (10 mL) was stirred at room temperature for 90 min., then the solvent was removed *in vacuo*, finally with toluene azeotrope. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> (10mL) and cooled to 0°C. Diisopropylethylamine (60 µL, 0.32 mmol) was added, then 3-chlorophenylisocyanate (43 µL, 0.35 mmol), and the mixture was stirred at 0°C for 2 hr. The mixture was then diluted with EtOAc and washed successively with 10% KHSO<sub>4</sub>, satd. KHCO<sub>3</sub>, H<sub>2</sub>O and brine, filtered (Whatman<sup>R</sup> 1PS phase separator) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v) to give the title compound (152 mg, 86%).

R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.31

**1f (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

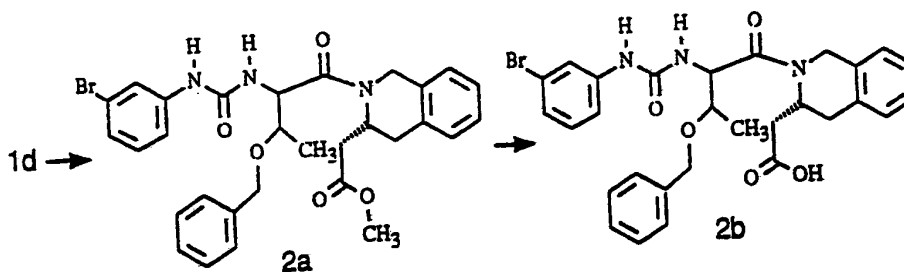
To a stirred solution of the ester 1e (152 mg, 0.27 mmol) in dioxan (10mL) was added a solution of LiOH (13 mg, 0.54 mmol) in H<sub>2</sub>O (5mL). The mixture was stirred at room temperature for 1 hr., then the solvent was removed *in vacuo*. The residue was partitioned between EtOAc and aq. KHSO<sub>4</sub>. The organic phase was washed with brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:1 v/v/v), and the product was taken up in acetonitrile/water and lyophilised to give the title compound (95 mg, 66%).

R<sub>f</sub> (EtOAc:hexane:AcOH 70:30:1 v/v/v) 0.20

HPLC System A t<sub>R</sub>=15.9' >99%

Mass spec (FAB) m/e=536 [M+H]<sup>+</sup>

## EXAMPLE 2



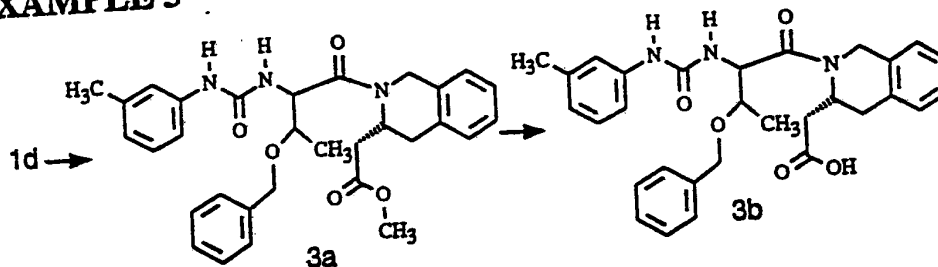
**2a** Methyl (3R)-2-[N-(3-bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.32 mmol scale using 1d and 3-bromophenylisocyanate. The product was isolated in 71% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).  
 $R_f$  (EtOAc:hexane 50:50 v/v) 0.30

**2b** (3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 2a on a 0.23 mmol scale following the method described for 1f. The product was isolated in 59% yield (79 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:1 v/v/v).  
 $R_f$  (EtOAc:hexane:AcOH 70:30:1 v/v/v) 0.20  
 HPLC System A  $t_R=16.1'$  >98%  
 Mass spec (FAB)  $m/e=582$   $[M+H]^+$

## EXAMPLE 3



**3a Methyl (3R)-2-[N-(3-methylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared following the method described for 1e on a 0.68 mmol scale using 1d and 3-methylphenylisocyanate. The product was isolated in 67% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R<sub>f</sub> (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.37

**3b (3R)-2-[N-(3-Methylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

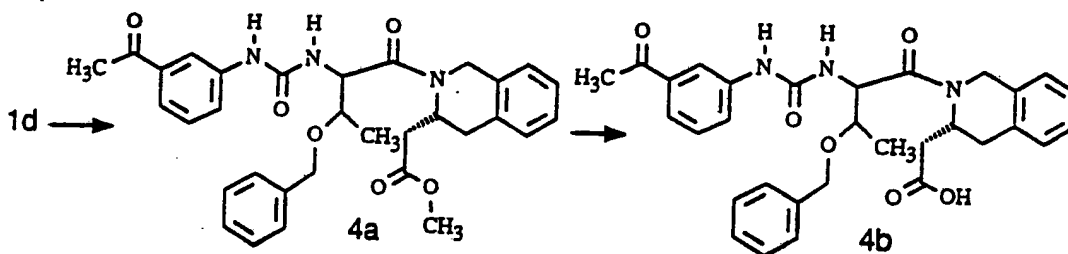
This was prepared from 3a on a 0.46 mmol scale following the method described for 1f. The product was isolated in 68% yield (162 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:1 v/v/v).

R<sub>f</sub> (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.20

HPLC System A t<sub>R</sub>=14.7' >99%

Mass spec (FAB) m/e=516 [M+H]<sup>+</sup>

#### EXAMPLE 4



**4a Methyl (3R)-2-[N-(3-acetylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared following the method described for 1e on a 0.21 mmol scale using 1d and 3-acetylphenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 45:55 v/v).

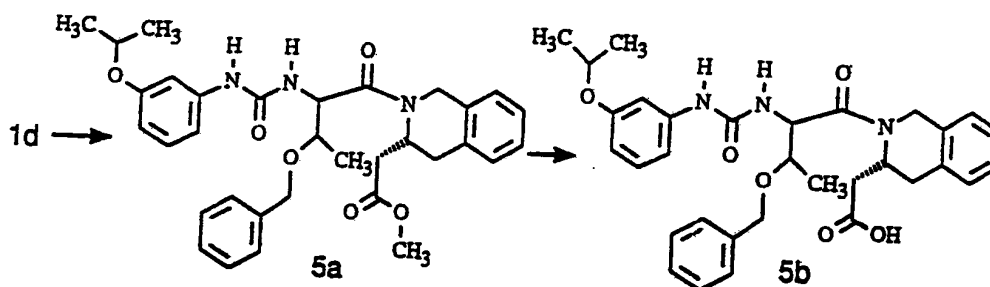
**4b** (3R)-2-[N-(3-Acetylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 4b on a 0.21 mmol scale following the method described for 1f. The product was isolated in 53% yield (61 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System B  $t_R$ =8.8' >95%

Mass spec (FAB)  $m/e$ =544  $[M+H]^+$

## EXAMPLE 5



**5a** Methyl (3R)-2-[N-(3-isopropoxyphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

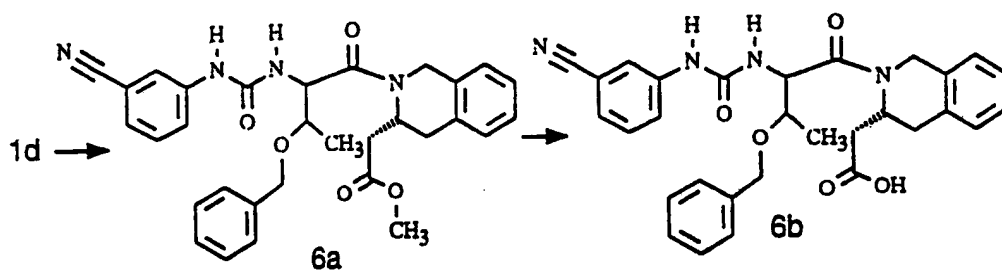
This was prepared following the method described for 1e on a 0.31 mmol scale using 1d and 3-isopropoxyphenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

**5b** (3R)-2-[N-(3-Isopropoxyphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 5a on a 0.31 mmol scale following the method described for 1f. The product was isolated in 40% yield (69 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:2 v/v/v).

HPLC System B  $t_R$ =12.5' >95%

Mass spec (FAB)  $m/e$ =560  $[M+H]^+$

**EXAMPLE 6**

**6a**      **Methyl**      **(3R)-2-[N-(3-cyanophenylcarbonyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

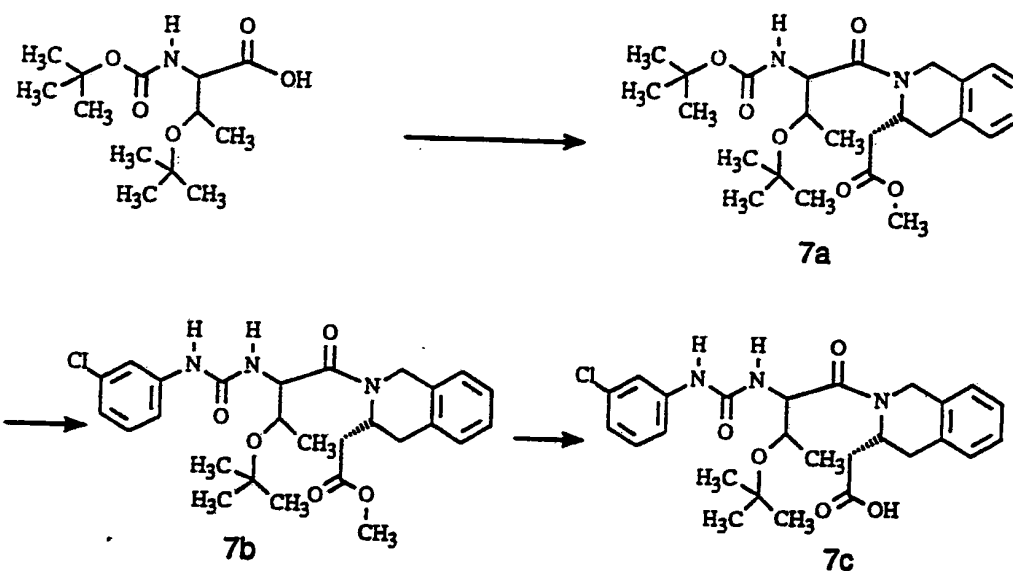
This was prepared following the method described for 1e on a 0.31 mmol scale using 1d and 3-cyanophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

**6b**      **(3R)-2-[N-(3-Cyanophenylcarbonyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 6a on a 0.31 mmol scale following the method described for 1f. The product was isolated in 34% yield (55 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R$ =13.3' 80%

Mass spec (FAB)  $m/e$ =527 [M+H]<sup>+</sup>

**EXAMPLE 7**

**7a** Methyl (3R)-2-[N-*tert*-butoxycarbonyl-O-*tert*-butyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 0.41 mmol scale using N-BOC-O-*tert*-butyl-threonine instead of N-BOC-O-benzyl-threonine. The product was isolated in 74% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**7b** Methyl (3R)-2-[N-(3-chlorophenylcarbonyl)-O-*tert*-butyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.30 mmol scale using 7a and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

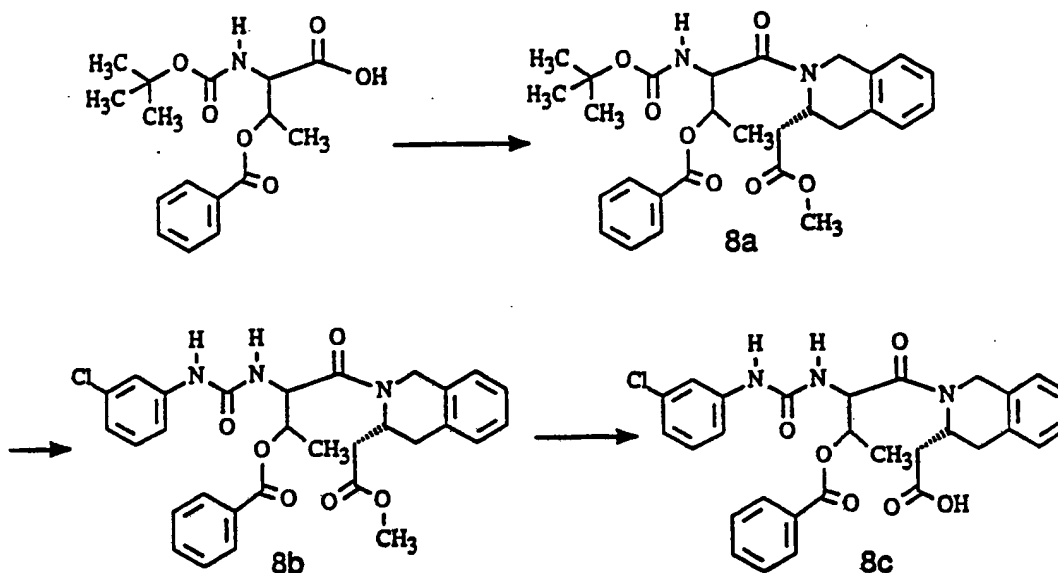
**7c** (3R)-2-[N-(3-Chlorophenylcarbonyl)-O-*tert*-butyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 7b on a 0.30 mmol scale following the method described for 1f. The product was isolated in 56% yield (84 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R$ =15.2' >95%

Mass spec (FAB)  $m/e$ =502  $[M+H]^+$

## EXAMPLE 8



**8a**      **Methyl**      (3R)-2-[N-*tert*-butyloxycarbonyl-O-benzoyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 0.50 mmol scale using N-BOC-O-benzoyl-threonine instead of N-BOC-O-benzyl-threonine. The product was isolated in 55% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**8b**      **Methyl**      (3R)-2-[N-(3-chlorophenylcarbamoyl)-O-benzoyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

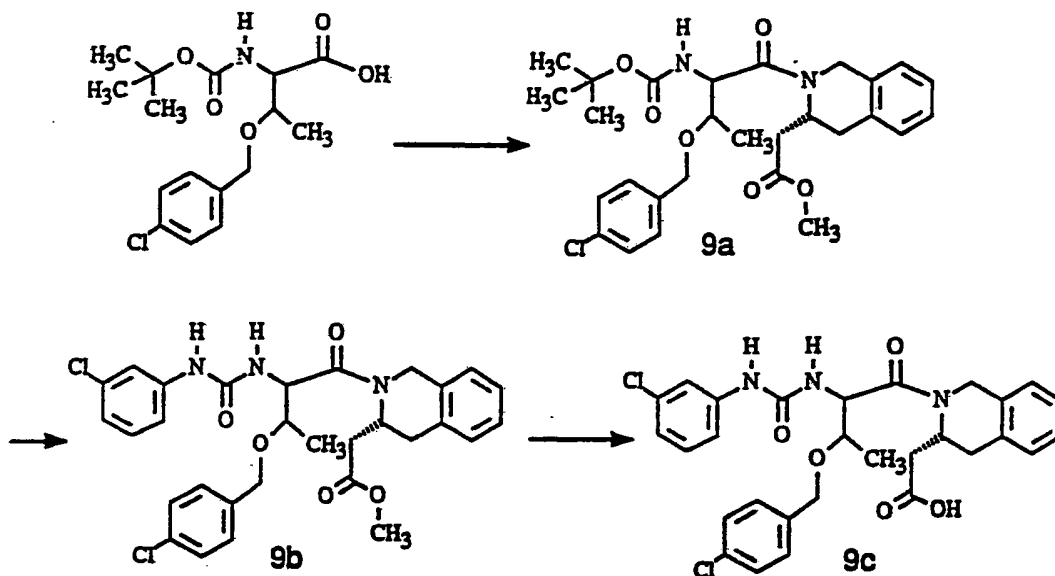
This was prepared following the method described for 1e on a 0.27 mmol scale using 8a and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

**8c**      (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzoyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 8b on a 0.27 mmol scale following the method described for 1f. The product was isolated in 35% yield (52 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:2 v/v/v).

HPLC System B  $t_R$ =12.2' >95%

Mass spec (FAB)  $m/e$ =550  $[M+H]^+$

**EXAMPLE 9**

**9a** Methyl (3R)-2-[N-*tert*-butyloxycarbonyl-O-(4-chlorobenzyl)-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 0.50 mmol scale using N-BOC-O-(4-chlorobenzyl)-threonine instead of N-BOC-O-benzyl-threonine. The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**9b** Methyl (3R)-2-[N-(3-chlorophenylcarbamoyl)-O-(4-chlorobenzyl)-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.35 mmol scale using 9a and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

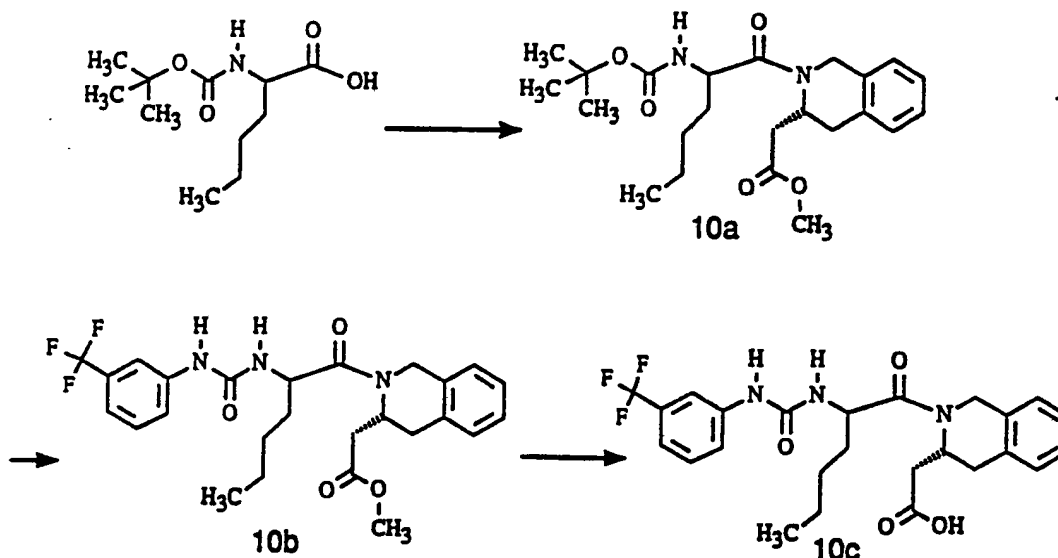
**9c** (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-(4-chlorobenzyl)-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 9b on a 0.35 mmol scale following the method described for 1f. The product was isolated in 64% yield (127 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R$ =18.0' >99%

Mass spec (FAB)  $m/e$ =570  $[M+H]^+$



**EXAMPLE 10**

**10a** Methyl (3R)-2-[(2S)-2-*tert*-butyloxycarbonylamino]hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 4.0 mmol scale using N-BOC-(2S)-2-aminohexanoic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 66% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**10b** Methyl (3R)-2-[(2S)-2-(3-trifluoromethylphenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.32 mmol scale using 10a and 3-trifluoromethylphenylisocyanate. The product was isolated in 52% after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:1 v/v/v).

$R_f$  (EtOAc:pet. ether:AcOH 30:70:1 v/v/v) 0.31

$^1\text{H}$  NMR  $\delta$  0.90 (3H,2t); 1.2-1.8 (m); 3.6 (3H,2s)

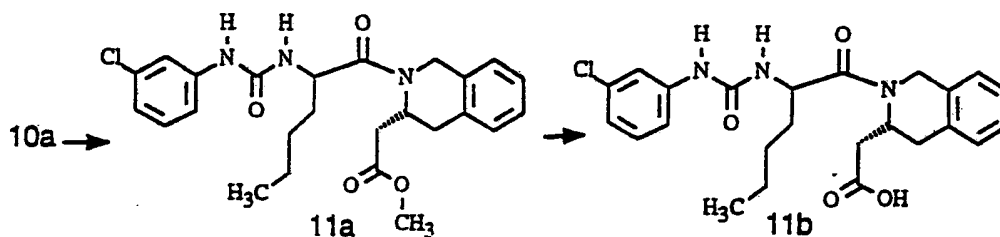
**10c** (3R)-2-[(2S)-2-(3-Trifluoromethylphenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 10b on a 0.16 mmol scale following the method described for 1f. The product was isolated in 70% yield (55 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System B  $t_R=12.2'$  >98%

Mass spec (FAB)  $m/e=492$   $[M+H]^+$

## EXAMPLE 11



**11a** Methyl (3R)-2-[(2S)-2-(3-chlorophenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.26 mmol scale using 10a and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

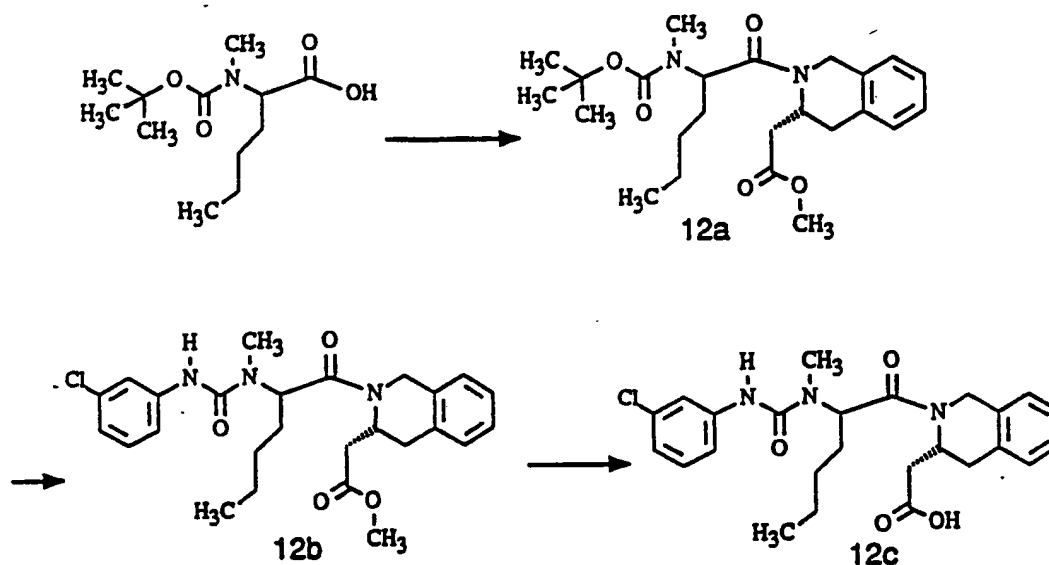
**11b** (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 11a on a 0.26 mmol scale following the method described for 1f. The product was isolated in 61% yield (73 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R=14.1'$  >98%

Mass spec (FAB)  $m/e=458$   $[M+H]^+$

## EXAMPLE 12



**12a** Methyl (3R)-2-[(2S)-2-(N-*tert*-butoxycarbonyl)methylaminohexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 0.40 mmol scale using N-BOC-(2S)-2-methylaminohexanoic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 57% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

**12b** Methyl (3R)-2-[(2S)-2-(N-(3-chlorophenylcarbamoyl)methylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

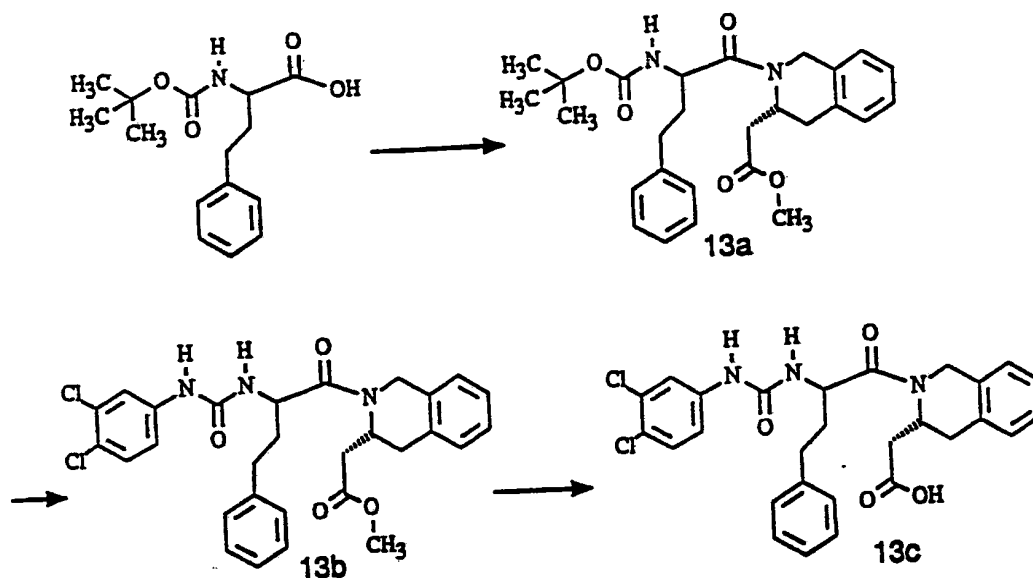
This was prepared following the method described for 1e on a 0.23 mmol scale using 12a and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

**12c** (3R)-2-[(2S)-2-(N-(3-Chlorophenylcarbamoyl)methylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 12b on a 0.23 mmol scale following the method described for 1f. The product was isolated in 44% yield (48 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R$ =14.8' >98%

Mass spec (FAB)  $m/e$ =472  $[M+H]^+$

**EXAMPLE 13**

**13a** Methyl (3R)-2-[(2S)-2-*tert*-butoxycarbonylamino-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 1.27 mmol scale using N-BOC-(2S)-2-amino-4-phenylbutanoic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 71% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 60:40 v/v).

$R_f$  (EtOAc:pet. ether 30:70 v/v) 0.19

**13b** Methyl (3R)-2-[(2S)-2-(3,4-dichlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.30 mmol scale using 13a and 3,4-dichlorophenylisocyanate. The product was isolated in 49% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:1 v/v/v).

$^1H$  NMR  $\delta$  3.74, 3.64, 3.61 (3H, 3s)

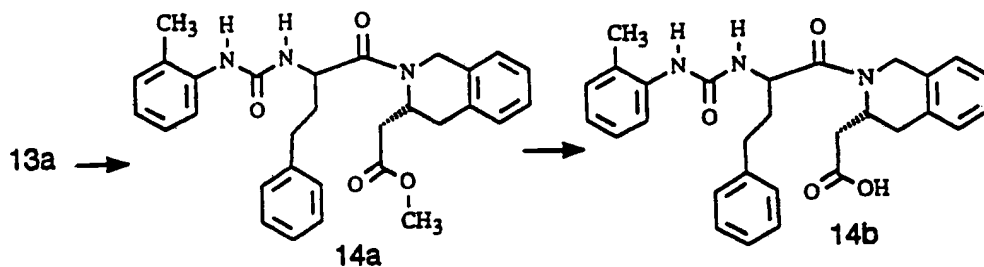
**13c** (3R)-2-[(2S)-2-(3,4-Dichlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 13b on a 0.15 mmol scale following the method described for 1f. The product was isolated in 76% yield (62 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:1 v/v/v).

HPLC System B  $t_R=14.4'$  80%

Mass spec (FAB)  $m/e=540$   $[M+H]^+$

### EXAMPLE 14



**14a** Methyl (3R)-2-[(2S)-2-(2-methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.33 mmol scale using 13a and 2-methylphenylisocyanate. The product was isolated in 85% yield and used without purification.

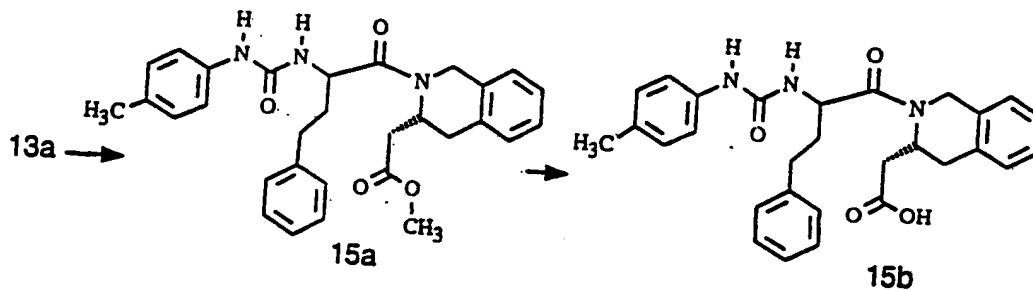
**14b** (3R)-2-[(2S)-2-(2-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 14a on a 0.28 mmol scale following the method described for 1f. The product was isolated in 58% yield (78 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:1 v/v/v).

HPLC System B  $t_R=10.3'$  >98%

Mass spec (FAB)  $m/e=486$   $[M+H]^+$

### EXAMPLE 15



40

**15a Methyl (3R)-2-[(2S)-2-(4-methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared following the method described for 1e on a 0.33 mmol scale using 13a and 4-methylphenylisocyanate. The product was isolated in 91% yield and used without purification.

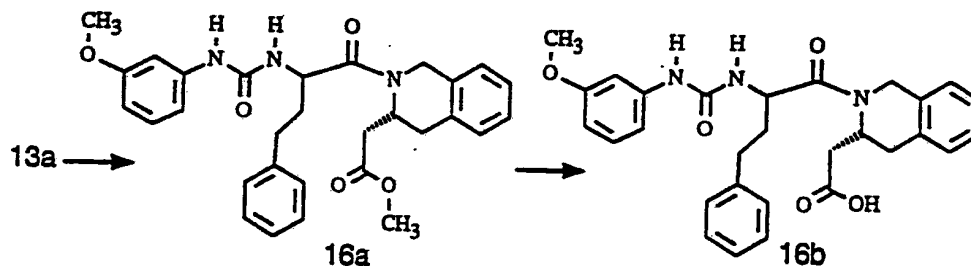
**15b (3R)-2-[(2S)-2-(4-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 15a on a 0.30 mmol scale following the method described for 1f. The product was isolated in 69% yield (101 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:1 v/v/v).

HPLC System B  $t_R=11.1'$  >97%

Mass spec (FAB)  $m/e=486$   $[M+H]^+$

## EXAMPLE 16



**16a Methyl (3R)-2-[(2S)-2-(3-methoxyphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared following the method described for 1e on a 0.20 mmol scale using 13a and 3-methoxyphenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 45:55 v/v).

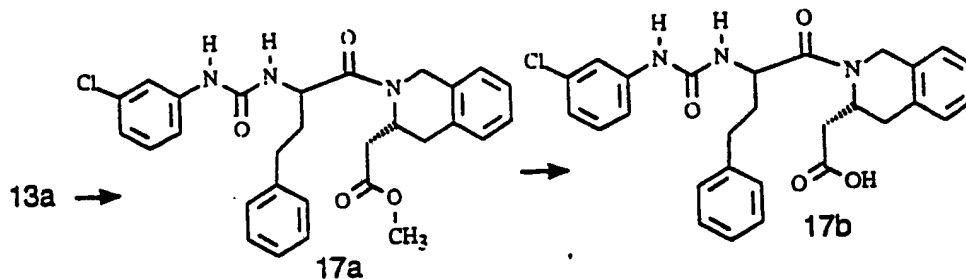
**16b (3R)-2-[(2S)-2-(3-Methoxyphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 16a on a 0.20 mmol scale following the method described for 1f. The product was isolated in 52% yield (52 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System A  $t_R=12.9'$  >99%

Mass spec (FAB)  $m/e=502$   $[M+H]^+$

## EXAMPLE 17



**17a** Methyl (3R)-2-[(2S)-2-(3-chlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.20 mmol scale using 13a and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 45:55 v/v).

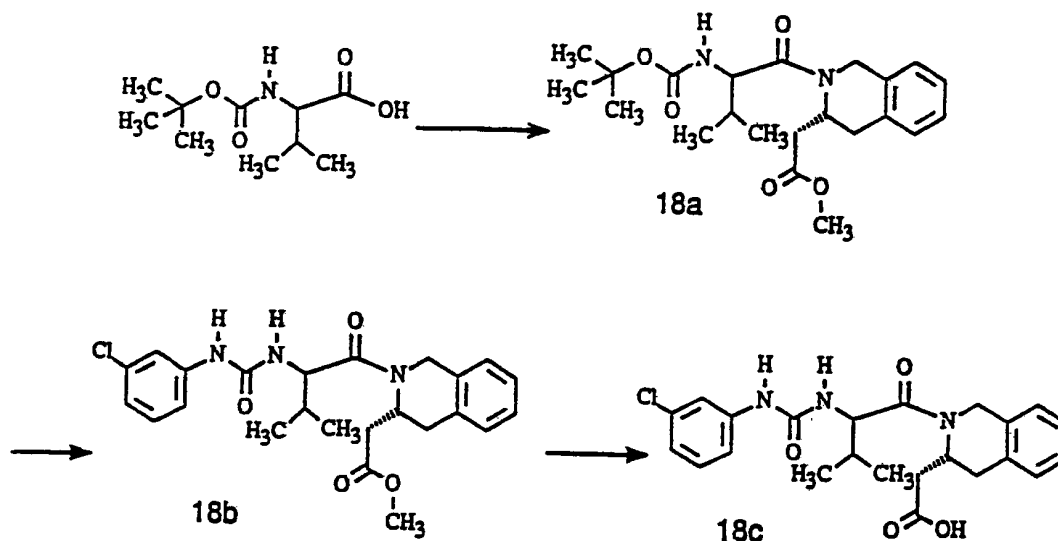
**17b** (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 17a on a 0.20 mmol scale following the method described for 1f. The product was isolated in 74% yield (75 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R=15.6'$  >98%

Mass spec (FAB)  $m/e=506$   $[M+H]^+$

## EXAMPLE 18



**18a** Methyl (3R)-2-[N-*tert*-butyloxycarbonyl-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 3.0 mmol scale using N-BOC-valine instead of N-BOC-O-benzyl-threonine. The product was isolated in 54% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

$R_f$  (EtOAc:hexane 20:80 v/v) 0.27

**18b** Methyl (3R)-2-[N-(3-chlorophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.47 mmol scale using 18a and 3-chlorophenylisocyanate. The product was isolated in 61% yield and used without purification.

$R_f$  (EtOAc:hexane 60:40 v/v) 0.33

**18c** (3R)-2-[N-(3-Chlorophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 18b on a 0.29 mmol scale following the method described for 1f. The product was isolated in 47% yield (60 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:2 v/v/v).

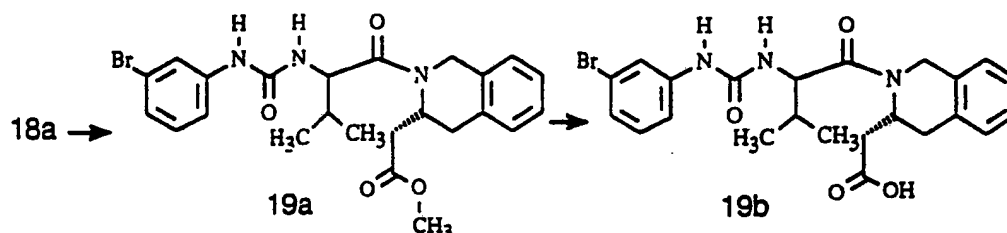
$R_f$  (EtOAc:hexane:AcOH 60:40:1 v/v/v) 0.23



HPLC System A  $t_R=11.9'$  >90%

Mass spec (FAB)  $m/e=444$   $[M+H]^+$

## EXAMPLE 19



**19a**            **Methyl**            **(3R)-2-[N-(3-bromophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared following the method described for 1e on a 0.47 mmol scale using 18a and 3-bromophenylisocyanate. The product was isolated in 61% yield and used without purification.

$R_f$  (EtOAc:hexane 60:40 v/v) 0.33

**19b**    **(3R)-2-[N-(3-Bromophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

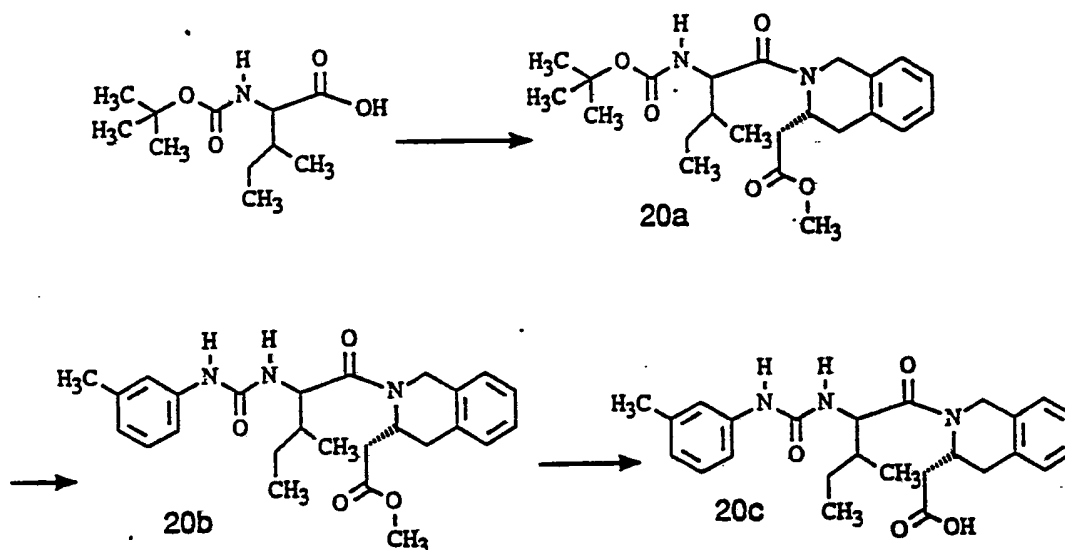
This was prepared from 19a on a 0.29 mmol scale following the method described for 1f. The product was isolated in 60% yield (85 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:2 v/v/v).

$R_f$  (EtOAc:hexane:AcOH 60:40:1 v/v/v) 0.24

HPLC System A  $t_R=12.5'$  >98%

Mass spec (FAB)  $m/e=489$   $[M+H]^+$

## EXAMPLE 20



**20a**            Methyl            (3R)-2-[N-*tert*-butyloxycarbonyl-isoleucyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 0.58 mmol scale using N-BOC-isoleucine instead of N-BOC-O-benzyl-threonine. The product was isolated in 56% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**20b**            Methyl            (3R)-2-[N-(3-methylphenylcarbamoyl)-isoleucyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

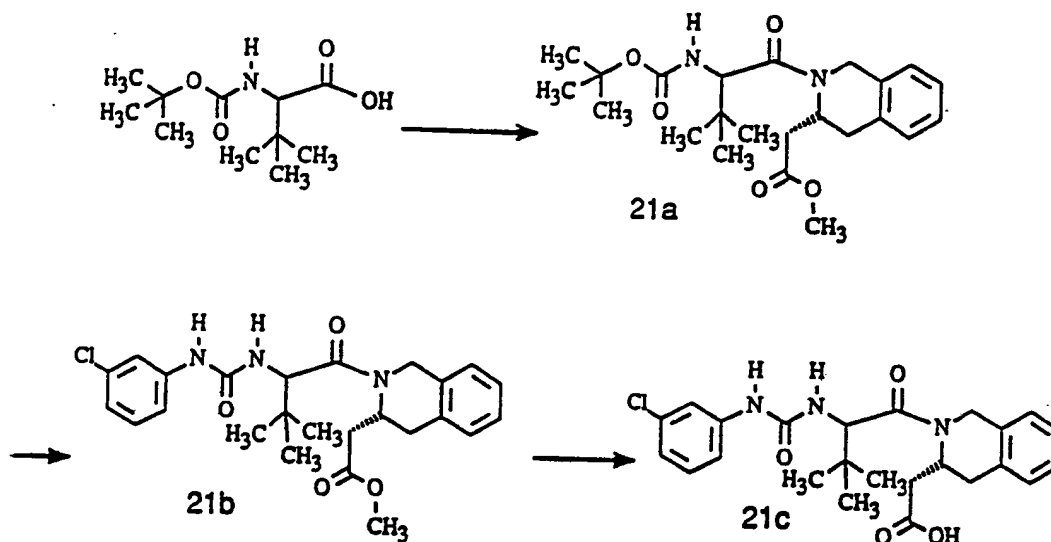
This was prepared following the method described for 1e on a 0.16 mmol scale using 20a and 3-methylphenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

**20c** (3R)-2-[N-(3-Methylphenylcarbamoyl)-isoleucyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 20b on a 0.16 mmol scale following the method described for 1f. The product was isolated in 70% yield (49 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R$ =12.4' >98%

Mass spec (FAB)  $m/e$ =438 [M+H]<sup>+</sup>

**EXAMPLE 21**

**21a** Methyl (3R)-2-[(2S)-2-*tert*-butoxycarbonylamino-3,3-dimethylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 0.75 mmol scale using N-BOC-(2S)-2-amino-3,3-dimethylbutanoic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 18% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**21b** Methyl (3R)-2-[(2S)-2-(3-chlorophenylcarbamoylamino)-3,3-dimethylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

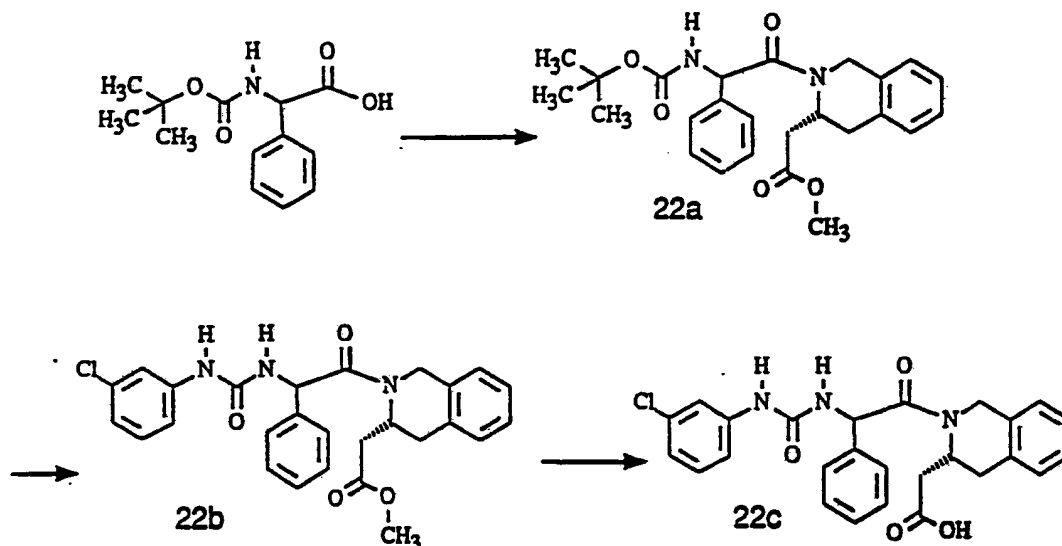
This was prepared following the method described for 1e on a 0.14 mmol scale using 21a and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

**21c** (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-3,3-dimethylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 21b on a 0.14 mmol scale following the method described for 1f. The product was isolated in 73% yield (47 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System B  $t_R$ =10.6' >99%

Mass spec (FAB)  $m/e$ =458  $[M+H]^+$

**EXAMPLE 22**

**22a** Methyl (3R)-2-[(S)- $\alpha$ -*tert*-butyloxycarbonylamino-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 0.50 mmol scale using N-BOC-(S)- $\alpha$ -amino-phenylacetic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**22b** Methyl (3R)-2-[(S)- $\alpha$ -(3-chlorophenylcarbamoylamino)-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.34 mmol scale using 22a and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

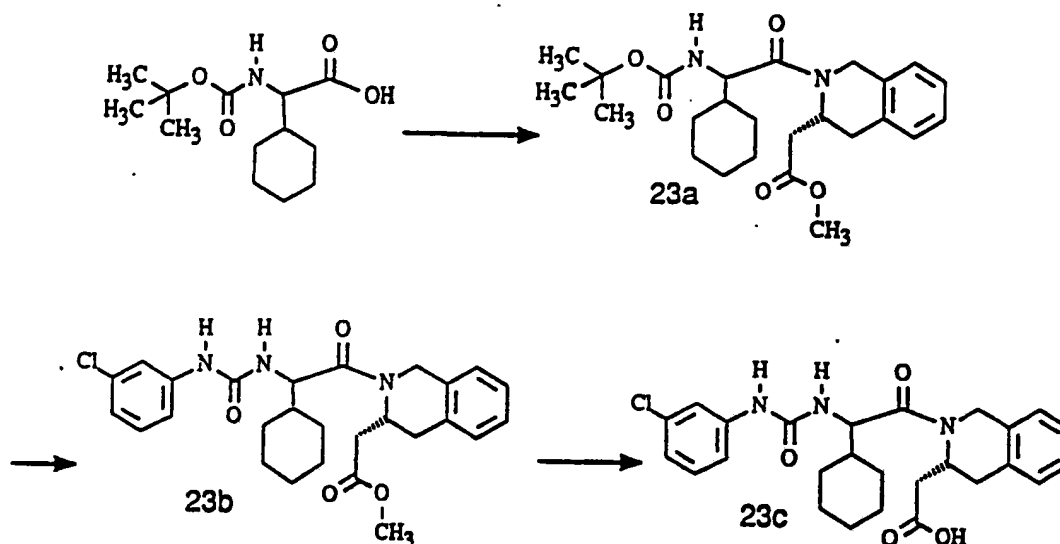
**22c** (3R)-2-[(S)- $\alpha$ -(3-Chlorophenylcarbamoylamino)-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 22b on a 0.34 mmol scale following the method described for 1f. The product was isolated in 64% yield (104 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R$ =13.8' >95%

Mass spec (FAB)  $m/e$ =478  $[M+H]^+$

## EXAMPLE 23



**23a** Methyl (3R)-2-[(S)- $\alpha$ -*tert*-butyloxycarbonylamino-cyclohexaneacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 2.0 mmol scale using N-BOC-(S)- $\alpha$ -amino-cyclohexaneacetic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 58% yield after flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

$R_f$  (EtOAc:hexane 20:80 v/v) 0.32

**23b** Methyl (3R)-2-[(S)- $\alpha$ -(3-methylphenylcarbamoylamino)-cyclohexaneacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.58 mmol scale using 23a and 3-methylphenylisocyanate. The product was isolated in 76% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

$R_f$  (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.43

**23c** (3R)-2-[(S)- $\alpha$ -(3-Methylphenylcarbamoylamino)-cyclohexaneacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

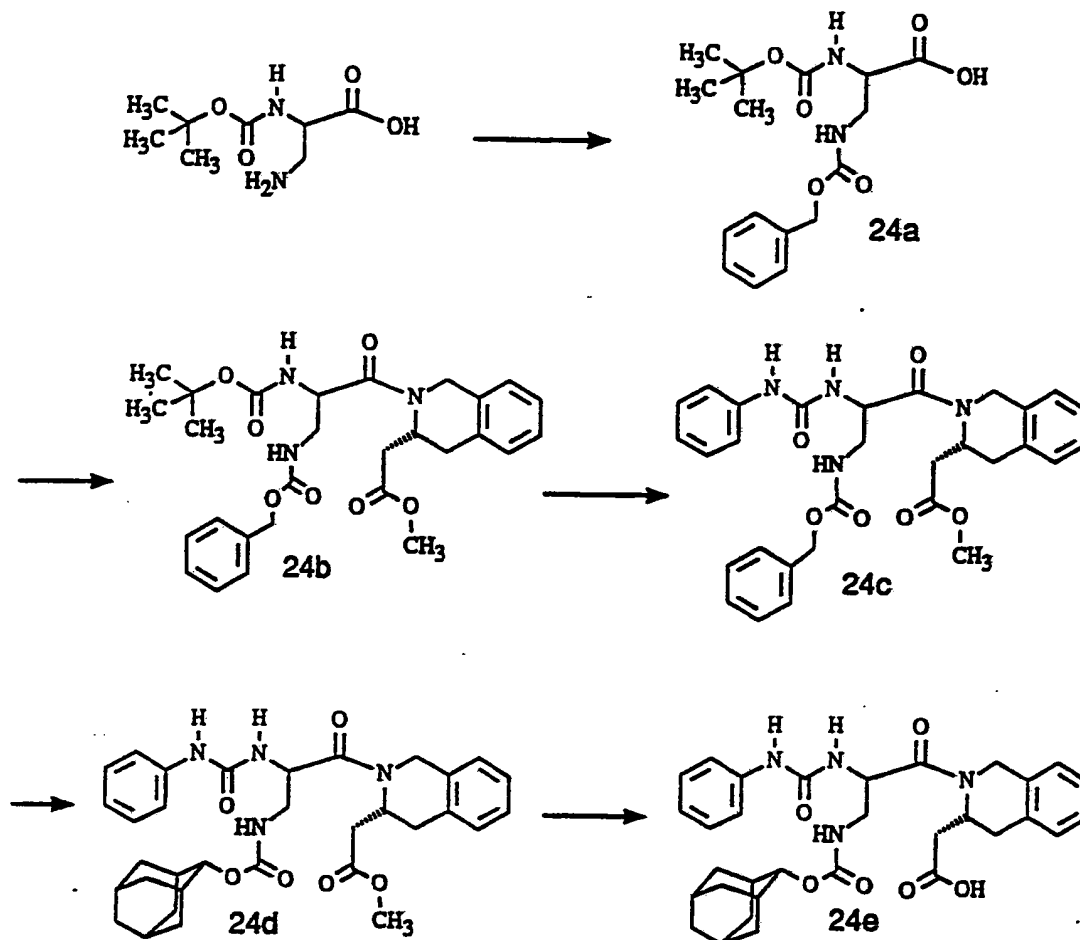
This was prepared from 23b on a 0.44 mmol scale following the method described for 1f. The product was isolated in 57% yield (117 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:2 v/v/v).

$R_f$  (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.21

HPLC System A  $t_R$ =14.3' >99%

Mass spec (FAB)  $m/e$ =464  $[M+H]^+$

## EXAMPLE 24



**24a** N $\alpha$ -tert-Butyloxycarbonyl-N $\omega$ -benzyloxycarbonyl-(2S)-2,3-diaminopropanoic acid.

To a stirred ice-cold solution of N $\alpha$ -BOC-L-diaminopropanoic acid (N. Kuchurczyk *et al.*, *Synth. Commun.* 19, 1603, 1989: 1.37 g, 6.74 mmol) in H<sub>2</sub>O (12 mL) was added a solution of NaOH (0.64 g, 13.5 mmol) in H<sub>2</sub>O, followed by benzyl chloroformate (1.08 mL, 7.3 mmol). The mixture was stirred and allowed to warm to room temperature over 3 hr., then the solvent was removed *in vacuo*. The residue was partitioned between EtOAc and dil KHSO<sub>4</sub>, and the organic layer was washed with brine, filtered (Whatman<sup>R</sup>

IPS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v) to give the title compound (1.94 g, 85%).

$^1\text{H}$  NMR  $\delta$  1.15 (9H,s); 3.45 (2H,br); 4.20 (1H,br); 5.00 (2H,s); 5.7 (2H,2br); 7.1-7.3 (5H,m)

**24b Methyl (3R)-2-[(2S)-3-benzyloxycarbonylamino-2-*tert*-butyloxycarbonylamino-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared following the method described for 1d on a 3.3 mmol scale using 24a instead of N-BOC-O-benzyl-threonine. The product was isolated in 76% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

$^1\text{H}$  NMR  $\delta$  1.4 (9H,2s); 3.6 (3H,2s); 7.1-7.4 (9H,m)

**24c Methyl (3R)-2-[(2S)-3-(benzyloxycarbonylamino)-2-(phenylcarbamoylamino)-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared following the method described for 1e on a 0.97 mmol scale using 24b and phenylisocyanate. The product was isolated in 98% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:2 v/v/v).

$R_f$  (EtOAc:pet. ether:AcOH 70:30:2 v/v/v) 0.37

**24d Methyl (3R)-2-[(2S)-3-(2-adamantyloxycarbonylamino)-2-(phenylcarbamoylamino)-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

To a solution of 24c (380 mg, 0.72 mmol) in MeOH (25 mL) was added 5% Pd-on-carbon (catalytic), and hydrogen was bubbled through the mixture at room temperature/1 atm. for 2 hr. The mixture was filtered through Celite<sup>®</sup> and the catalyst was washed with MeOH. The combined filtrates were concentrated *in vacuo*, finally with toluene azeotrope. The residue was taken up in  $\text{CH}_2\text{Cl}_2$  (10 mL) and 2-adamantyl chloroformate (0.8 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added dropwise with stirring, followed by diisopropylethylamine (excess). The mixture was stirred at room temperature for 12 hr. then poured into EtOAc. The solution was washed successively with 10%  $\text{KHSO}_4$ , satd.  $\text{KHCO}_3$ ,  $\text{H}_2\text{O}$  and brine, filtered (Whatman<sup>®</sup> IPS phase separator) and concentrated *in vacuo*. The residue was used without further purification.

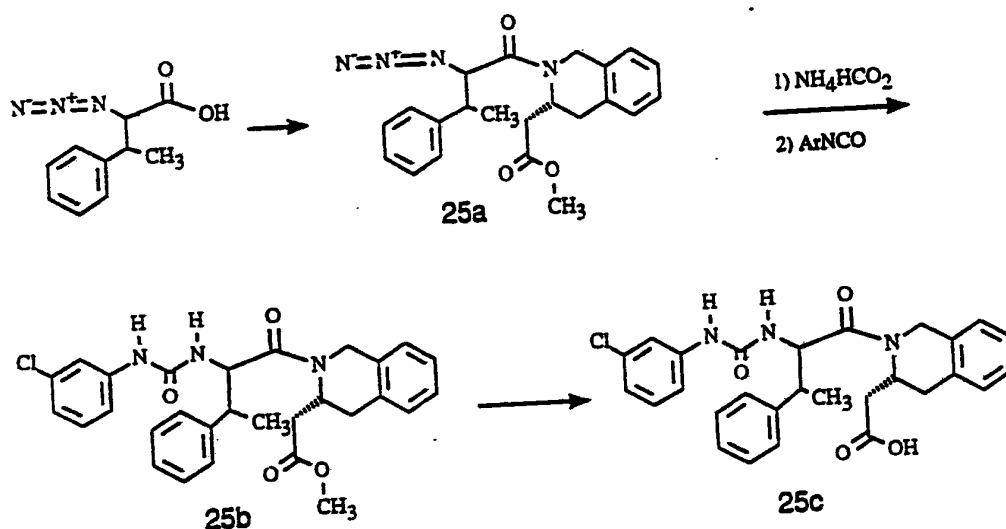
**24e** (3R)-2-[(2S)-3-(2-Adamantyloxycarbonylamino)-2-(phenylcarbamoylamino)-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **24d** on a 0.21 mmol scale following the method described for **1f**. The product was isolated in 52% yield (66 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System B  $t_R=12.5'$  >98%

Mass spec (FAB)  $m/e=575$   $[M+H]^+$

## EXAMPLE 25



**25a** Methyl (3R)-2-[(2S,3R)-2-azido-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 1.72 mmol scale using (2S,3R)-2-azido-3-phenylbutanoic acid (R. Dharanipragada *et al.*, *Tetrahedron Lett.*, 30, 6841, 1989) instead of N-BOC-O-benzyl-threonine. The product was isolated in 62% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

**25b** Methyl (3R)-2-[(2S,3R)-2-(3-chlorophenylcarbamoylamino)-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

To a degassed solution of **25a** (271 mg, 0.69 mmol) in MeOH/CH<sub>2</sub>Cl<sub>2</sub> (20 mL + 3 mL) was added NH<sub>4</sub><sup>+</sup>HCO<sub>2</sub><sup>-</sup> (174 mg, 0.28 mmol) and 5% Pd-on-carbon (50 mg). The mixture was stirred at room temperature for 5 hr. then filtered through Celite<sup>®</sup>. The residue was washed with MeOH and the combined filtrates were concentrated *in vacuo*. The



residue was taken up in  $\text{CH}_2\text{Cl}_2$ , washed successively with 5%  $\text{KHCO}_3$  and brine, dried over  $\text{Na}_2\text{SO}_4$ , and the solvent evaporated *in vacuo* to give methyl (3R)-2-[(2S,3R)-2-amino-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

One third of the product (*ca.* 0.23 mmol) was taken up in  $\text{CH}_2\text{Cl}_2$  and treated with 3-chlorophenylisocyanate as described for 1e. The product was isolated in 15% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

$R_f$  (EtOAc:pet. ether 30:70 v/v) 0.12

$^1\text{H NMR}$   $\delta$  1.29-1.42 (3H,m); 3.44,3.74 (3H,2s)

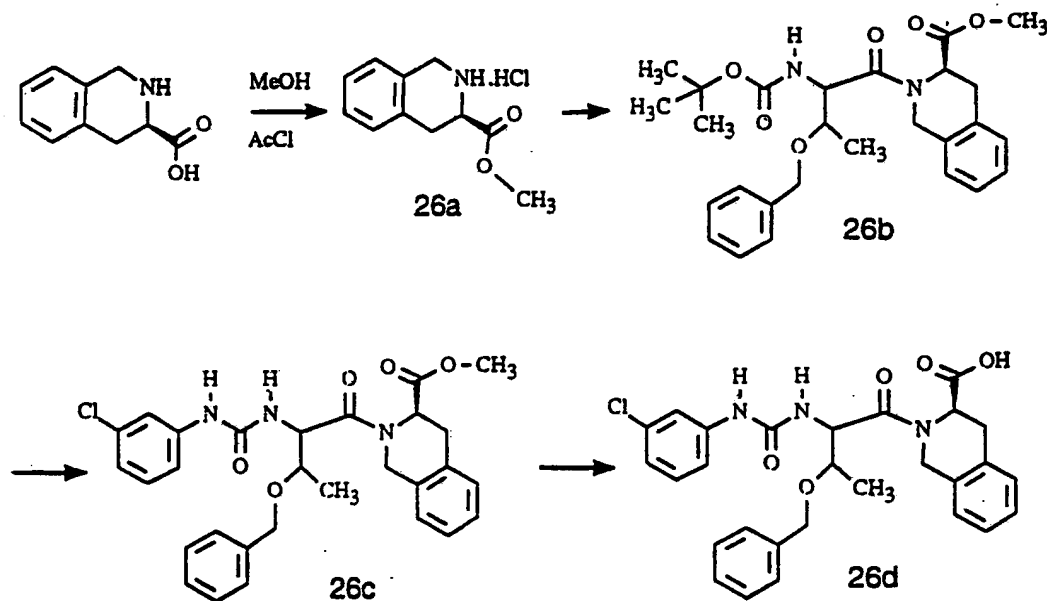
**25c** (3R)-2-[(2S,3R)-2-(3-Chlorophenylcarbamoylamino)-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 25b on a 0.035 mmol scale following the method described for 1f. The product was isolated in 88% yield (15 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:1 v/v/v).

HPLC System B  $t_R=11.9'$  >95%

Mass spec (FAB)  $m/e=506$   $[\text{M}+\text{H}]^+$

## EXAMPLE 26



**26a** Methyl (3R)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride.

To a stirred suspension of D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5g, 28 mmol) in MeOH (60 mL) was added acetyl chloride (3.2 mL, 45 mmol), and the mixture

was heated at reflux under  $N_2$  for 4 hr. The solvent was removed *in vacuo*, and the residue was partitioned between EtOAc and aq.  $KHCO_3$ . The organic layer was washed with brine, filtered (Whatman<sup>R</sup> IPS phase separator), acidified with 4N HCl in dioxan (10 mL), and concentrated *in vacuo*. The residue was washed with pet. ether and dried over KOH to give the title compound as a white powder (3.73 g, 58%).

**26b Methyl (3R)-2-[N-*tert*-butoxycarbonyl-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared following the method described for 1d on a 2.4 mmol scale using 26a instead of 1c. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**26c Methyl (3R)-2-[N-(3-chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared following the method described for 1e on a 0.53 mmol scale using 26b and 3-chlorophenylisocyanate. The product was isolated in 98% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

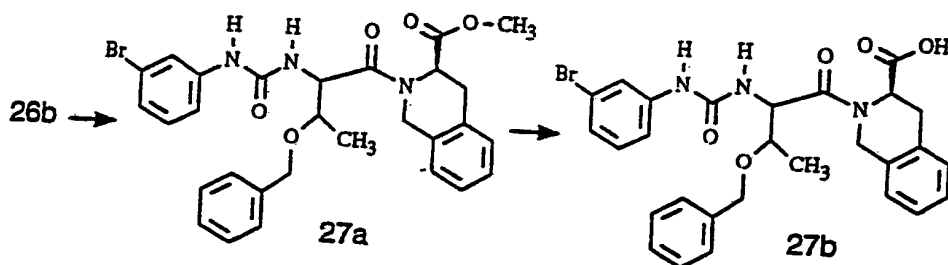
**26d (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 26c on a 0.52 mmol scale following the method described for 1f. The product was isolated in 32% yield (84 mg) after repeated flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v and  $CHCl_3$ :MeOH:AcOH 100:1:1 v/v/v).

HPLC System A  $t_R$ =16.0' >99%

Mass spec (FAB)  $m/e$ =522  $[M+H]^+$

## EXAMPLE 27



**27a Methyl (3R)-2-[N-(3-bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared following the method described for 1e on a 0.53 mmol scale using 26b and 3-bromophenylisocyanate. The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

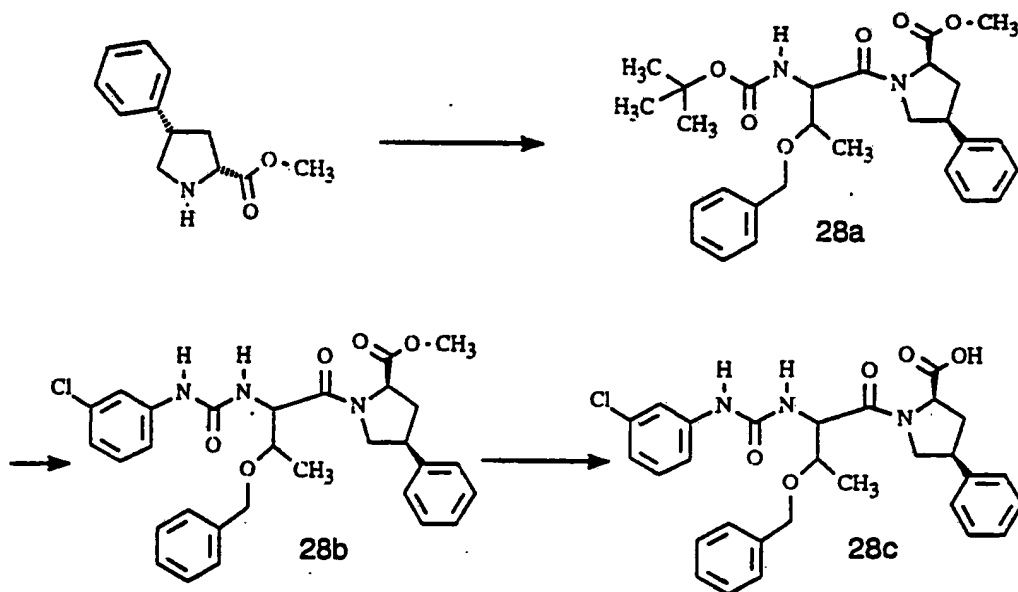
**27b (3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 27a on a 0.43 mmol scale following the method described for 1f. The product was isolated in 34% yield (82 mg) after repeated flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v and  $\text{CHCl}_3$ :MeOH:AcOH 100:1:1 v/v/v).

HPLC System A  $t_R$ =16.5' >99%

Mass spec (FAB)  $m/e$ =566/568  $[\text{M}+\text{H}]^+$

## EXAMPLE 28



**28a Methyl (2R,4S)-1-[N-*tert*-butyloxycarbonyl-O-benzyl-threonyl]-4-phenylpyrrolidine-2-carboxylate.**

This was prepared following the method described for 1d on a 0.36 mmol scale using methyl (2R,4R)-4-phenylpyrrolidine-2-carboxylate (J. Krapcho *et al.* *J. Med. Chem.*,

31.1148.1988) instead of 1c. The product was isolated in 82% yield and used without purification.

R<sub>f</sub> (EtOAc:pet. ether 40:60 v/v) 0.30

**28b Methyl (2R,4S)-1-[N-(3-chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-carboxylate.**

This was prepared following the method described for 1e on a 0.30 mmol scale using 28a and 3-chlorophenylisocyanate. The product was isolated in 77% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

R<sub>f</sub> (EtOAc:pet. ether 40:60 v/v) 0.20

<sup>1</sup>H NMR δ 1.29 (3H,d,J=6.2Hz); 3.63 (3H,s)

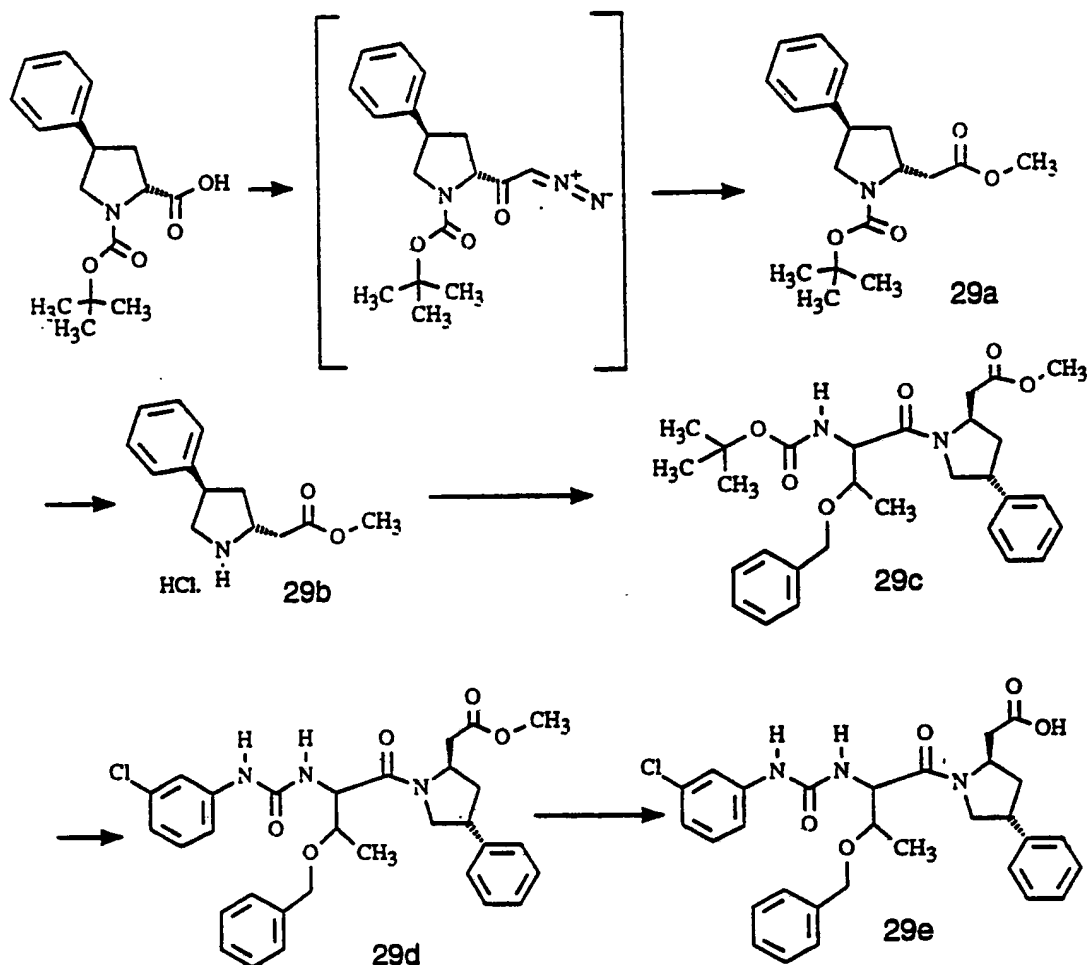
**28c (2R,4S)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-carboxylic acid.**

This was prepared from 28b on a 0.23 mmol scale following the method described for 1f. The product was isolated in 35% yield (40 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 30:70:1 v/v/v).

HPLC System B t<sub>R</sub>=18.2' >95%

Mass spec (FAB) m/e=536 [M+H]<sup>+</sup>

## EXAMPLE 29

**29a Methyl (2R,4R)-1-tert-butyloxycarbonyl-4-phenylpyrrolidine-2-acetate.**

This was prepared in a manner analogous to that used to prepare 1b using (2R,4S)-1-tert-butyloxycarbonyl-4-phenylpyrrolidine-2-carboxylic acid (J. Krapcho *et al.*, *J. Med. Chem.*, 31,1148,1988: 400 mg, 1.37 mmol). The product was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v) in a yield of 64%.

**29b Methyl (2R,4R)-4-phenylpyrrolidine-2-acetate hydrochloride.**

This was prepared from 29a (0.4 mmol) using the same procedure as for 1b, assuming a yield of 100%.

**29c Methyl (2R,4R)-1-[N-*tert*-butoxycarbonyl-O-benzyl-threonyl]-4-phenylpyrrolidine-2-acetate.**

This was prepared following the method described for 1d on a 0.38 mmol scale using 29b instead of 1c. The product was isolated in 75% yield and used without purification.

R<sub>f</sub> (EtOAc:pet. ether 50:50 v/v) 0.40

<sup>1</sup>H NMR δ 1.44 (9H,s); 3.67 (3H,s)

**29d Methyl (2R,4R)-1-[N-(3-chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-acetate.**

This was prepared following the method described for 1e on a 0.28 mmol scale using 29c and 3-chlorophenylisocyanate. The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

R<sub>f</sub> (EtOAc:pet. ether 40:60 v/v) 0.16

<sup>1</sup>H NMR δ 1.28 (3H,d,J=5.9Hz); 3.59 (3H,s)

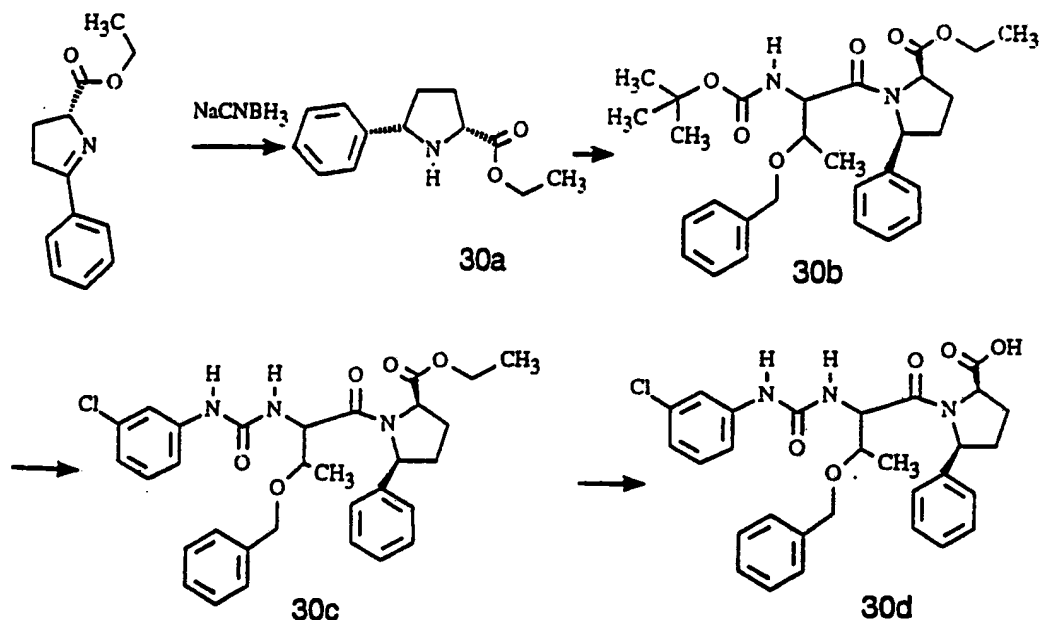
**29e (2R,4R)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-acetic acid.**

This was prepared from 29d on a 0.20 mmol scale following the method described for 1f. The product was isolated in 69% yield (64 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:1 v/v/v).

HPLC System B t<sub>R</sub>=13.1' >97%

Mass spec (FAB) m/e=550 [M+H]<sup>+</sup>

## EXAMPLE 30

**30a Ethyl (2R,5S)-5-phenylpyrrolidine-2-carboxylate.**

To a solution of ethyl (2R)-3,4-dihydro-5-phenyl-2H-pyrrole-2-carboxylate (J. Ackermann *et al.*, *Helv.Chim.Acta*, 75, 122, 1990: 1.7 g, 7.8 mmol) and AcOH (5mL) in MeOH (50 mL) was added NaCNBH<sub>3</sub> (1.5 g, 23.5 mmol). The mixture was stirred overnight at room temperature and then concentrated *in vacuo*. The residue was partitioned between EtOAc and satd. KHCO<sub>3</sub>, and the organic phase was washed with H<sub>2</sub>O and brine, filtered (Whatman<sup>®</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet ether 25:75 then 40:60) to give the title compound (0.90 g, 40%).

**30b Ethyl (2R,5S)-1-[N-tert-butyloxycarbonyl-O-benzyl-threonyl]-5-phenylpyrrolidine-2-carboxylate.**

This was prepared following the method described for 1d on a 0.82 mmol scale using 30a instead of 1c. The product was isolated in 38% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R<sub>f</sub> (EtOAc:hexane 30:70 v/v) 0.17

**30c Ethyl (2R,5S)-1-[N-(3-chlorophenylcarbamoyl)-O-benzyl-threonyl]-5-phenylpyrrolidine-2-carboxylate.**

This was prepared following the method described for 1e on a 0.31 mmol scale using 30b and 3-chlorophenylisocyanate. The product was isolated in 80% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

$R_f$  (EtOAc:hexane 30:70 v/v) 0.18

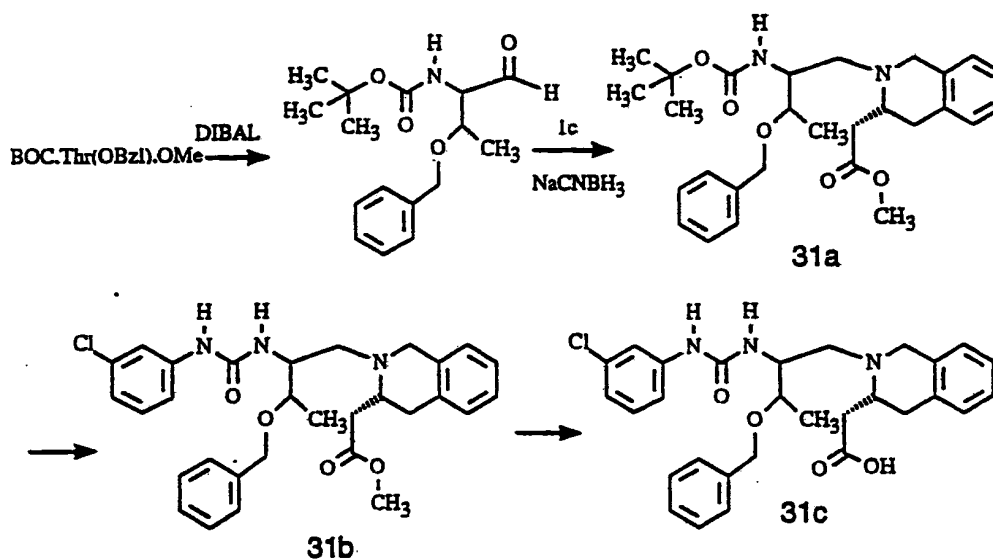
**30d (2R,5S)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-5-phenylpyrrolidine-2-carboxylic acid.**

This was prepared from 30c on a 0.25 mmol scale following the method described for 1f. The product was isolated in 12% yield (16 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:1 v/v/v).

HPLC System A  $t_R$ =18.0' >97%

Mass spec (FAB)  $m/e$ =536  $[M+H]^+$

### EXAMPLE 31



**31a Methyl (3R)-2-[(2S,3R)-3-benzyloxy-2-tert-butyloxycarbonylamino-butyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

To a solution of N-BOC-O-benzyl-threonine methyl ester (585 mg, 1.81 mmol) in toluene (10 mL) cooled under N<sub>2</sub> to -78°C was added dropwise DIBAL (3.5 mL, 1.5M in toluene, 5.25 mmol). The mixture was stirred at -78°C for 40 min. then excess DIBAL was quenched by the careful addition of MeOH (1 mL). The mixture was allowed to



warm to room temperature and then poured into a vigorously stirred mixture of Et<sub>2</sub>O and satd. Rochelle salt. The mixture was stirred for 2 hr., then the phases were separated. The aqueous layer was extracted once with Et<sub>2</sub>O, and the combined organic phases were washed with H<sub>2</sub>O and brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated *in vacuo* to give N-BOC-O-benzyl-threoninal (509 mg, 96%).

A solution of this aldehyde (435 mg, 1.43 mmol) in MeOH/AcOH (99:1, 10 mL) was added at 0°C to a solution of the free base obtained from 1c (268 mg, 1.1 mmol) in MeOH/AcOH (99:1, 10 mL). The mixture was stirred at 0°C for 15 min., then NaCNBH<sub>3</sub> (115 mg, 1.9 mmol) was added in portions over 15 min. and the mixture was stirred for a further 30 min. before being allowed to warm to room temperature. The solvent was removed *in vacuo*. The residue was taken up in EtOAc and washed successively with 10% KHSO<sub>4</sub>, satd. KHCO<sub>3</sub>, H<sub>2</sub>O and brine, filtered (Whatman<sup>R</sup> 1PS phase separator) and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80) to give the title compound (232 mg, 41%).

**31b Methyl (3R)-2-[(2S,3R)-3-benzyloxy-2-(3-chlorophenylcarbamoylamino)-butyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

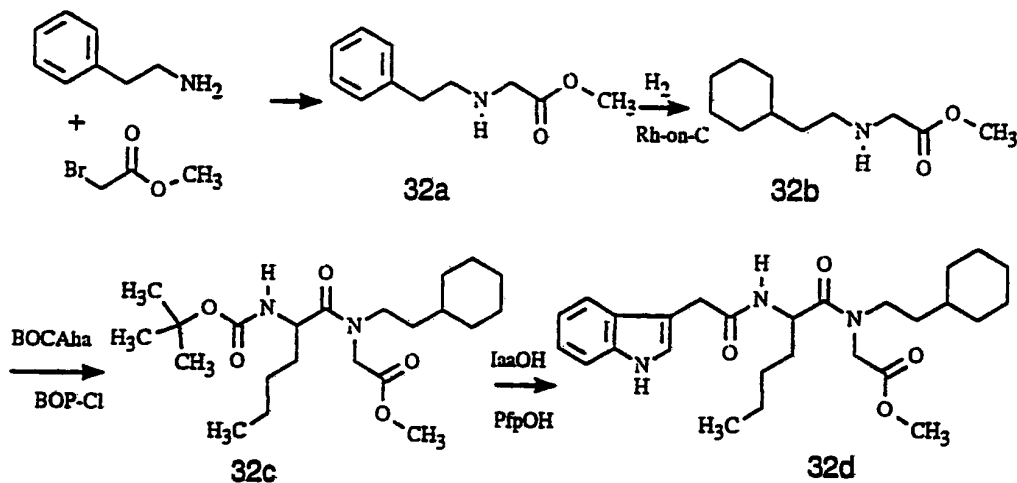
This was prepared following the method described for 1e on a 0.23 mmol scale using 31a and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

**31c (3R)-2-[(2S,3R)-3-Benzyloxy-2-(3-chlorophenylcarbamoylamino)-butyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 31b on a 0.23 mmol scale following the method described for 1f. The product was isolated in 46% yield (55 mg) after flash chromatography on silica gel (eluant CHCl<sub>3</sub>:MeOH:AcOH 40:2:1 v/v/v).

HPLC System B *t<sub>R</sub>*=16.4' >98%

Mass spec (FAB) *m/e*=522 [M+H]<sup>+</sup>

**EXAMPLE 32****32a Methyl N-(phenethyl)-glycinate.**

To a stirred solution of phenethylamine (2.51 mL, 20 mmol) in MeCN (50 mL) was added diisopropylethylamine (2.59 mL, 20 mmol),  $\text{K}_2\text{CO}_3$  (1 g, excess), and methyl bromoacetate (1.9 mL, 20 mmol). The mixture was stirred at room temperature for 3 hr. and then concentrated *in vacuo*. The residue was taken up in EtOAc and the solution was washed successively with 5%  $\text{KHCO}_3$ ,  $\text{H}_2\text{O}$  and brine, filtered (Whatman<sup>®</sup> IPS phase separator), and concentrated *in vacuo* to give the title product (3.0 g, 77%) as an oil which was used without further purification.

**32b Methyl N-(2-cyclohexylethyl)-glycinate.**

To a solution of 32a (55 mmol) in AcOH (100 mL) was added 5% Rh-on-carbon catalyst (0.75 g) and the mixture was shaken under  $\text{H}_2$  (40 psi) for 7 days. The catalyst was removed by filtration, toluene was added to the filtrate, and the solvents were evaporated *in vacuo*. The residue was taken up in 1M HCl and washed with EtOAc. The aqueous phase was saturated with  $\text{NaHCO}_3$  and extracted twice with EtOAc. The combined extracts were washed with brine, filtered (Whatman<sup>®</sup> IPS phase separator), and concentrated *in vacuo* to give the title product (1.90 g, 61%) as an oil which was used without further purification.

**32c Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-glycinate.**

To a stirred solution of (2S)-2-*tert*-butyloxycarbonylaminohexanoic acid (978 mg, 4.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added diisopropylethylamine (0.74 mL, 4.2 mmol). The solution was cooled to -20°C and BOP-Cl (1.08 g, 4.2 mmol) was added. The solution was stirred at 20°C for 20 min., then amine 32b (0.60 g, 3.03 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 16 hr. then the solvent was evaporated *in vacuo*. The residue was taken up in EtOAc and the solution was washed with 0.3M KHSO<sub>4</sub>, satd. KHCO<sub>3</sub>, H<sub>2</sub>O and brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v) to give the title compound (310 mg, 24%).

R<sub>f</sub> (EtOAc:hexane 25:75 v/v) 0.16

**32d Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycinate.**

A solution of the BOC-protected compound 32c (310 mg, 0.75 mmol) in 4N HCl in dioxan (20 mL) was stirred at room temperature for 1 hr then concentrated *in vacuo*, finally with toluene azeotrope.

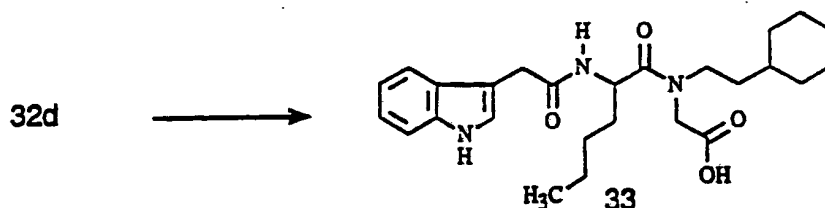
Meanwhile, to a stirred solution of 3-indoleacetic acid (184 mg, 1.05 mmol) and pentafluorophenol (202 mg, 1.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL), cooled to 0°C, was added water-soluble carbodiimide (WSCD.HCl, Peptide Inst. Inc., 287 mg, 1.5 mmol). The mixture was stirred at 0°C for 1 hr, then the residue from the above HCl deprotection was added, followed by diisopropylethylamine (0.13 mL, 0.75 mmol) and the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was taken up in EtOAc. The solution was washed with 0.3M KHSO<sub>4</sub>, satd. KHCO<sub>3</sub>, H<sub>2</sub>O and brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:1 v/v/v) to give the title compound (148 mg, 42%). A part of this was taken up in MeCN/H<sub>2</sub>O and lyophilised.

R<sub>f</sub> (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.17

HPLC System A t<sub>R</sub>=18.8' >98%

AAA Peptide content=80%

Mass spec (FAB) m/e=470 [M+H]<sup>+</sup>

**EXAMPLE 33**

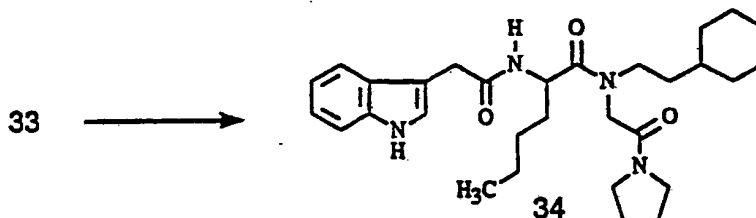
**33 N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycine.**

This was prepared from 32d on a 0.35 mmol scale following the method described for 1f. The product was isolated in 53% yield (85 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 75:25:2 v/v/v).

HPLC System A  $t_R$ =14.6' >99%

AAA Peptide content=76%

Mass spec (FAB)  $m/e$ =455  $[M+Na]^+$

**EXAMPLE 34**

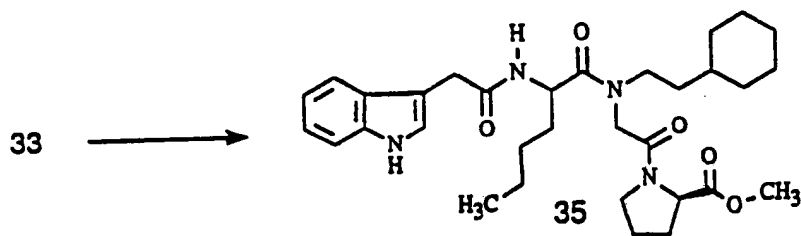
**34 1-[N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl]-pyrrolidine.**

To a stirred solution of 33 (86 mg, 0.19 mmol) and hydroxybenzotriazole (33 mg, 0.25 mmol) in  $CH_2Cl_2$  (8 mL), cooled to 0°C, was added WSCD.HCl (73 mg, 0.38 mmol). The mixture was stirred at 0°C for 1 hr., then pyrrolidine (50  $\mu$ L, 0.57 mmol) was added. The mixture was stirred at 0°C for a further 2 hrs. then at room temperature overnight. The solvent was removed *in vacuo*, and the residue was taken up in EtOAc. The solution was washed with 0.3M  $KHSO_4$ , satd.  $KHCO_3$ ,  $H_2O$  and brine, filtered (Whatman<sup>®</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v) and lyophilised from MeCN/ $H_2O$  to give the title compound (36 mg, 36%).

HPLC System A  $t_R$ =17.8' >98%

AAA Peptide content=80%

Mass spec (FAB)  $m/e$ =509  $[M+H]^+$

**EXAMPLE 35**

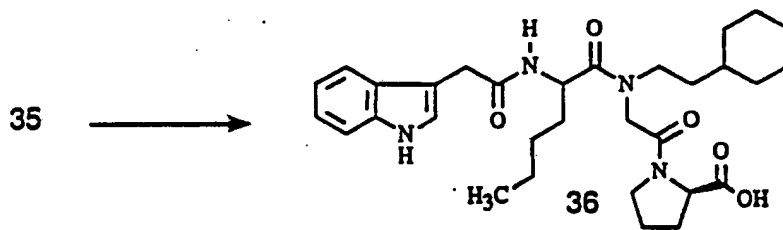
**35 Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-prolinate.**

This was prepared from 33 on a 0.27 mmol scale following the method described for 34 using D-ProOMe instead of pyrrolidine. The product was isolated in 68% yield (105 mg) after flash chromatography on silica gel (eluant EtOAc:hexane 95:5 v/v).

HPLC System A  $t_R$ =14.1' >80%

AAA Aha 0.99; Pro 1.01; Peptide content=76%

Mass spec (FAB)  $m/e$ =567  $[M+H]^+$

**EXAMPLE 36**

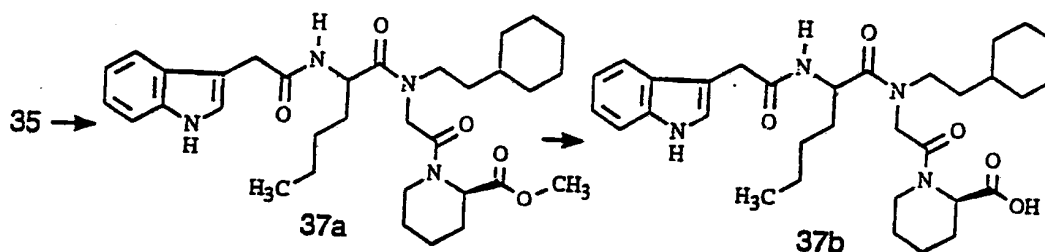
**36 N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-proline.**

This was prepared from 35 on a 0.21 mmol scale following the method described for 1f. The product was isolated in 45% yield (51 mg) after flash chromatography on silica gel (eluant  $CHCl_3$ :MeOH:AcOH 40:2:1 v/v/v).

HPLC System A  $t_R$ =15.4' >99%

AAA Aha 1.00; Pro 1.00; Peptide content=72%

Mass spec (FAB)  $m/e$ =552  $[M+K]^+$

**EXAMPLE 37**

**37a Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-pipecolate.**

This was prepared from 33 on a 0.27 mmol scale following the method described for 34 using methyl D-pipecolate instead of pyrrolidine. The product was isolated in 85% yield after flash chromatography on silica gel (eluant EtOAc:hexane 85:15 v/v).  
 $R_f$  (EtOAc:hexane 95:5 v/v) 0.32

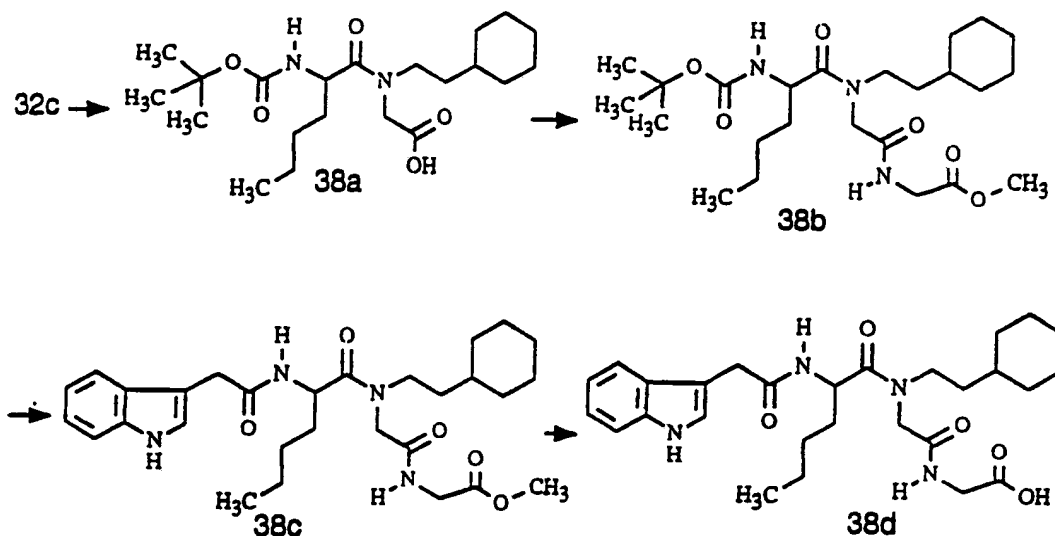
**37b N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-pipecolic acid.**

This was prepared from 37a on a 0.17 mmol scale following the method described for 1f. The product was isolated in 10% yield (10 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A  $t_R$ =17.6' >80%

AAA Peptide content=74%

Mass spec (FAB)  $m/e$ =567  $[M+H]^+$

**EXAMPLE 38**

**38a** N-(2-Cyclohexylethyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-glycine.

This was prepared from 32c on a 1.82 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**38b** Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-glycyl}-glycinate.

This was prepared from 38a on a 0.91 mmol scale following the method described for 34 using GlyOMe instead of pyrrolidine. The product was used without purification, assuming a yield of 100%.

$R_f$  (EtOAc:pet. ether 75:25 v/v) 0.59

**38c** Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl)-hexanoyl)-glycyl}-glycinate.

This was prepared from 38b on a 0.91 mmol scale following the method described for 32d using hydroxybenzotriazole instead of pentafluorophenol. The product was isolated in 44% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v then neat EtOAc).

**38d** N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-glycine.

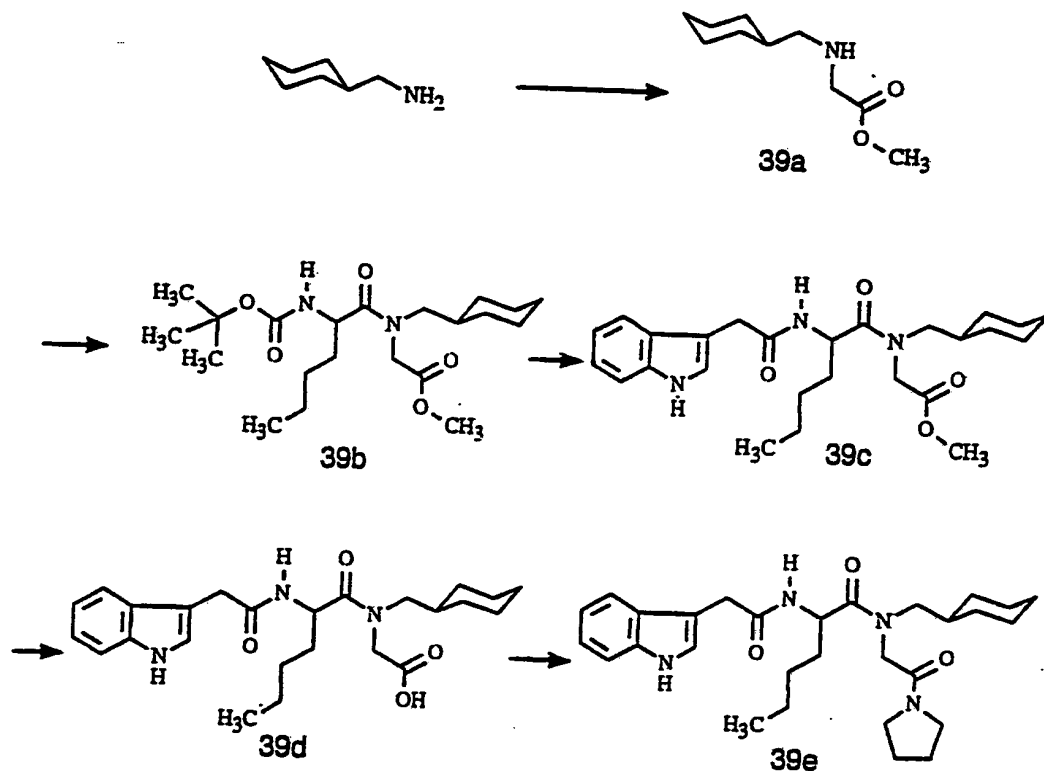
This was prepared from 38c on a 0.40 mmol scale following the method described for 1f. The product was isolated in 49% yield (105 mg) after flash chromatography on silica gel (eluant EtOAc:MeOH:AcOH 100:4:4 v/v/v).

HPLC System A  $t_R=10.0'$  >98%

AAA Peptide content=79%

Mass spec (FAB)  $m/e=535$   $[M+Na]^+$

### EXAMPLE 39



**39a** Methyl N-(cyclohexylmethyl)-glycinate.

This was prepared from cyclohexylmethylamine on a 3.0 mmol scale following the method described for 32a. The product was used without purification, assuming a yield of 100%.



**39b Methyl N-(cyclohexylmethyl)-N-((2S)-2-(*tert*-butoxycarbonylamino)-hexanoyl)-glycinate.**

This was prepared from 39a on a 3.0 mmol scale following the method described for 32c. The product was isolated in 52% yield after flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

$R_f$  (EtOAc:hexane 25:75 v/v) 0.23

**39c Methyl N-(cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycinate.**

This was prepared from 39b on a 1.6 mmol scale following the method described for 32d. The product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:1 v/v/v).

$R_f$  (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.20

**39d N-(Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycine.**

This was prepared from 39c on a 1.1 mmol scale following the method described for 1f. The product was isolated in 22% yield after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

$R_f$  (EtOAc:AcOH 100:2 v/v) 0.18

**39e 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-pyrrolidine.**

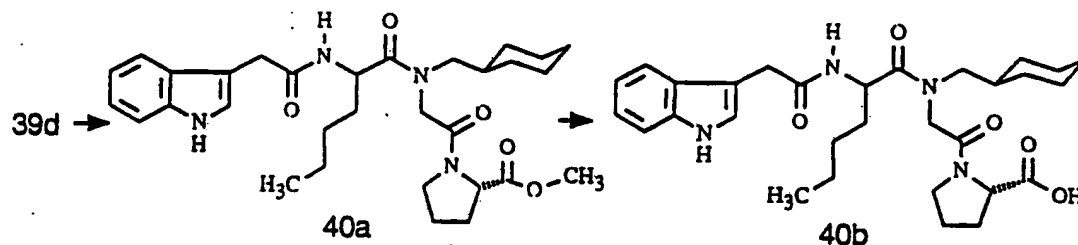
This was prepared from 39d on a 0.48 mmol scale following the method described for 34. The product was isolated in 44% yield (109 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A  $t_R$ =15.4' >99%

AAA Peptide content=83%

Mass spec (FAB)  $m/e$ =495  $[M+H]^+$

**EXAMPLE 40**



**40a Methyl 1-{N-(2-cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-prolinate.**

This was prepared from 39d on a 0.23 mmol scale following the method described for 34 using ProOMe instead of pyrrolidine. The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc).

$R_f$  (EtOAc:hexane 90:10 v/v) 0.14

**40b 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-proline.**

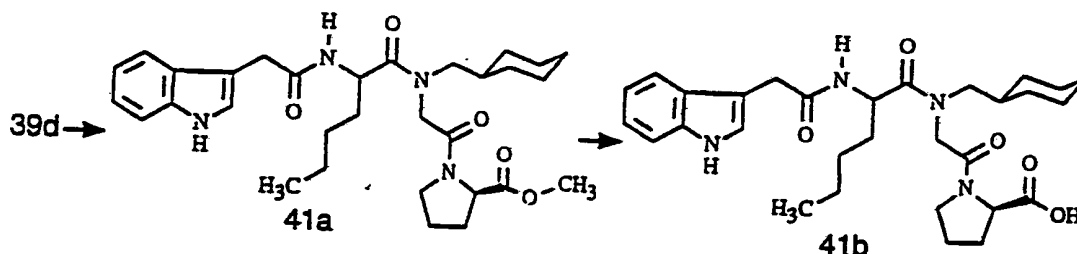
This was prepared from 40a on a 0.16 mmol scale following the method described for 1f. The product was isolated in 45% yield (38 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A  $t_R$ =11.8' >99%

AAA Aha 1.01; Pro 0.99; Peptide content=81%

Mass spec (FAB)  $m/e$ =561  $[M+Na]^+$

**EXAMPLE 41**



**41a Methyl 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-prolinate.**

This was prepared from 39d on a 0.23 mmol scale following the method described for 34 using D-ProOMe instead of pyrrolidine. The product was isolated in 48% yield after flash chromatography on silica gel (eluant EtOAc).

$R_f$  (EtOAc:hexane 90:10 v/v) 0.14

**41b 1-[N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl]-D-proline.**

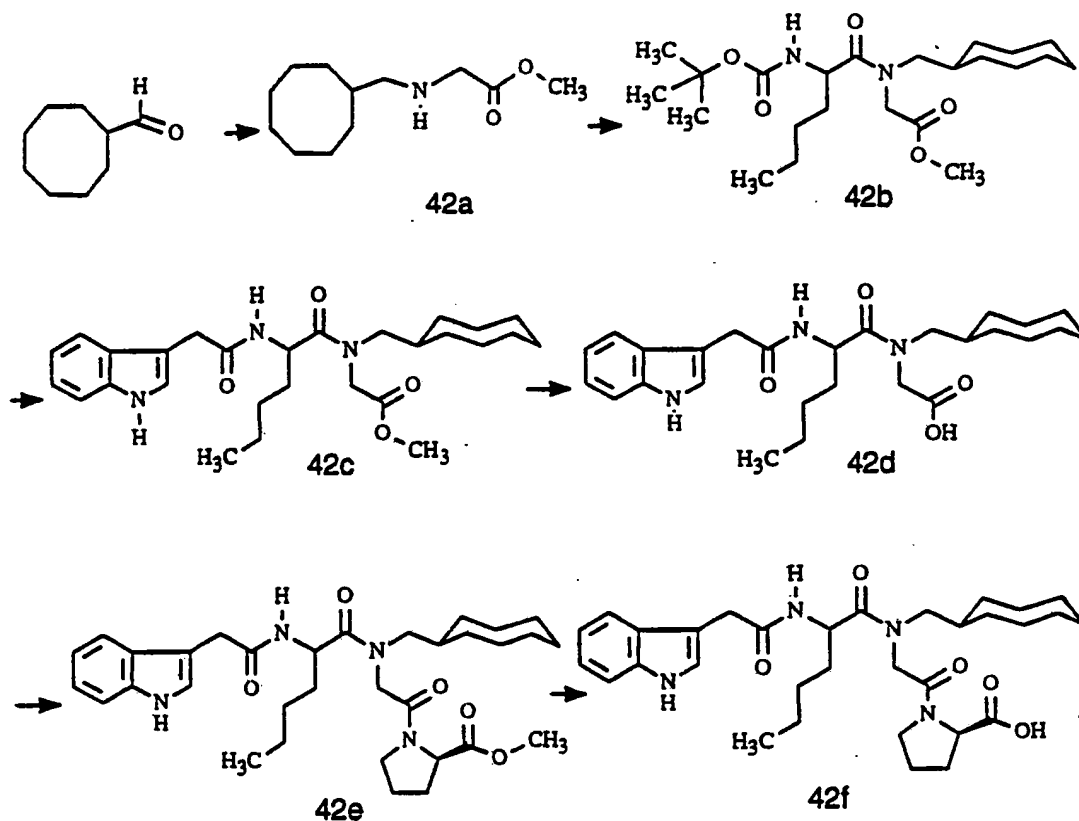
This was prepared from 41a on a 0.11 mmol scale following the method described for 1f. The product was isolated in 52% yield (30 mg) after flash chromatography on silica gel (eluant CHCl<sub>3</sub>:MeOH:AcOH 40:2:1 v/v/v).

HPLC System A  $t_R$ =12.1' >99%

AAA Aha 0.98: Pro 1.02: Peptide content=84%

Mass spec (FAB)  $m/e$ =561 [M+Na]<sup>+</sup>

**EXAMPLE 42**



**42a Methyl N-(cyclooctylmethyl)-glycinate.**

To a stirred solution of cyclooctanecarboxaldehyde (0.70 g, 5 mmol) and GlyOMe.HCl (0.75 g, 6 mmol) in MeOH (50 mL) at room temperature was added AcOH (2 mL), diisopropylethylamine (1.04 mL, 6 mmol) and NaCNBH<sub>3</sub> (0.75 g, 12 mmol). The mixture was stirred at room temperature for 4 hr., then the solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc and satd. KHCO<sub>3</sub>. The organic

phase was washed with H<sub>2</sub>O and brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc) to give the title compound (500 mg, 47%).

R<sub>f</sub> (EtOAc) 0.47

<sup>1</sup>H NMR δ 2.42 (2H,d,J=6Hz); 3.35 (2H,s); 3.68 (3H,s)

**42b Methyl N-(cyclooctylmethyl)-N-((2S)-2-(*tert*-butoxycarbonylamino)-hexanoyl)-glycinate.**

This was prepared from 42a on a 2.35 mmol scale following the method described for 32c. The product was isolated in 99% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75).

R<sub>f</sub> (EtOAc:pet. ether 25:75 v/v) 0.41

**42c Methyl N-(cyclooctylmethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycinate.**

This was prepared from 42b on a 2.35 mmol scale following the method described for 38c. The product was isolated in 79% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

R<sub>f</sub> (EtOAc:pet. ether 65:35 v/v) 0.46

HPLC System A t<sub>R</sub>=16.3'

<sup>1</sup>H NMR Major rotamer δ 4.45 (1H,d,J=17Hz); 5.15 (1H,m)

Minor rotamer δ 4.15 (1H,d,J=17Hz); 4.55 (1H,d,J=17Hz); 4.90 (1H,m)

Mass spec (FAB) m/e=484 [M+H]<sup>+</sup>

**42d N-(Cyclooctylmethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycine.**

This was prepared from 42c on a 1.86 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

HPLC System A t<sub>R</sub>=12.6'

Mass spec (FAB) m/e=470 [M+H]<sup>+</sup>

**42e Methyl 1-{N-(cyclooctylmethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-D-prolinate.**

This was prepared from 42d on a 1.49 mmol scale following the method described for 33 using D-ProOMe instead of pyrrolidine. The product was isolated in 50% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 80:20 v/v).

HPLC System A  $t_R=14.8'$

Mass spec (FAB)  $m/e=581$   $[M+H]^+$

**42f 1-(N-(Cyclooctylmethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl)-D-proline.**

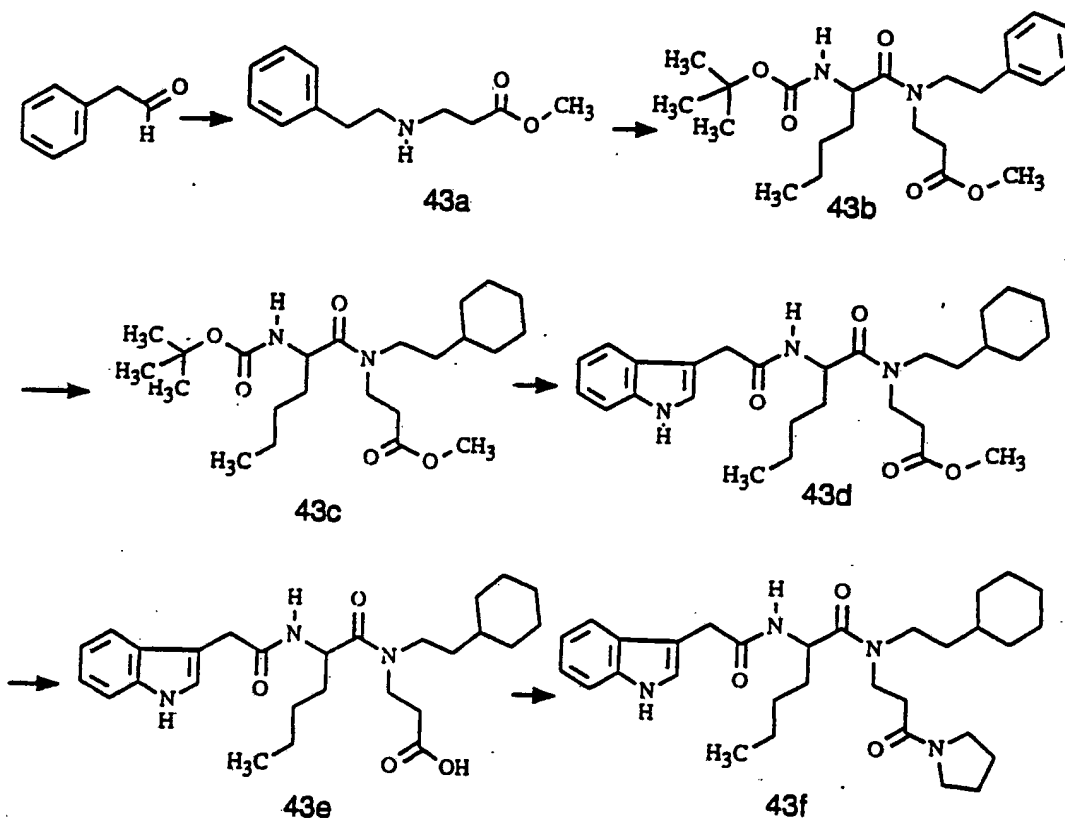
This was prepared from 42e on a 0.62 mmol scale following the method described for 1f. The product was isolated in 79% yield (276 mg) without purification.

HPLC System A  $t_R=12.0'$  >98%

AAA Aha 1.01; Pro 0.99; Peptide content=84%

Mass spec (FAB)  $m/e=567$   $[M+H]^+$

**EXAMPLE 43**



**43a Methyl 3-(phenethylamino)-propanoate.**

This was prepared from phenylacetaldehyde and  $\beta$ -AlaOMe on a 5.0 mmol scale following the method described for 42a. The product was isolated in 68% yield and used without further purification.

**43b Methyl 3-{N-(phenethyl)-N-((2S)-2-(*tert*-butoxycarbonylamino)-hexanoyl)-amino}-propanoate.**

This was prepared from 43a on a 3.4 mmol scale following the method described for 32c. The product was isolated in 42% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**43c Methyl 3-{N-(2-cyclohexylethyl)-N-((2S)-2-(*tert*-butoxycarbonylamino)-hexanoyl)-amino}-propanoate.**

This was prepared from 43b on a 1.43 mmol scale following the method described for 32b. After evaporating the solvent the product was taken up in EtOAc and washed with satd.  $\text{KHCO}_3$ ,  $\text{H}_2\text{O}$  and brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and the solvent removed *in vacuo*. The product was used without further purification, assuming a yield of 100%.

**43d Methyl 3-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-amino}-propanoate.**

This was prepared from 43c on a 1.43 mmol scale following the method described for 38c. The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 65:35 v/v).

**43e 3-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-amino}-propanoic acid.**

This was prepared from 43d on a 0.91 mmol scale following the method described for 1f. The product was isolated in 66% yield after flash chromatography (eluant EtOAc:pet.ether:AcOH 80:20:2 v/v/v).

HPLC System A  $t_R$ =12.3'

Mass spec (FAB)  $m/e$ =470  $[\text{M}+\text{H}]^+$

**43f 1-{3-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-amino}-propanoyl}-pyrrolidine.**

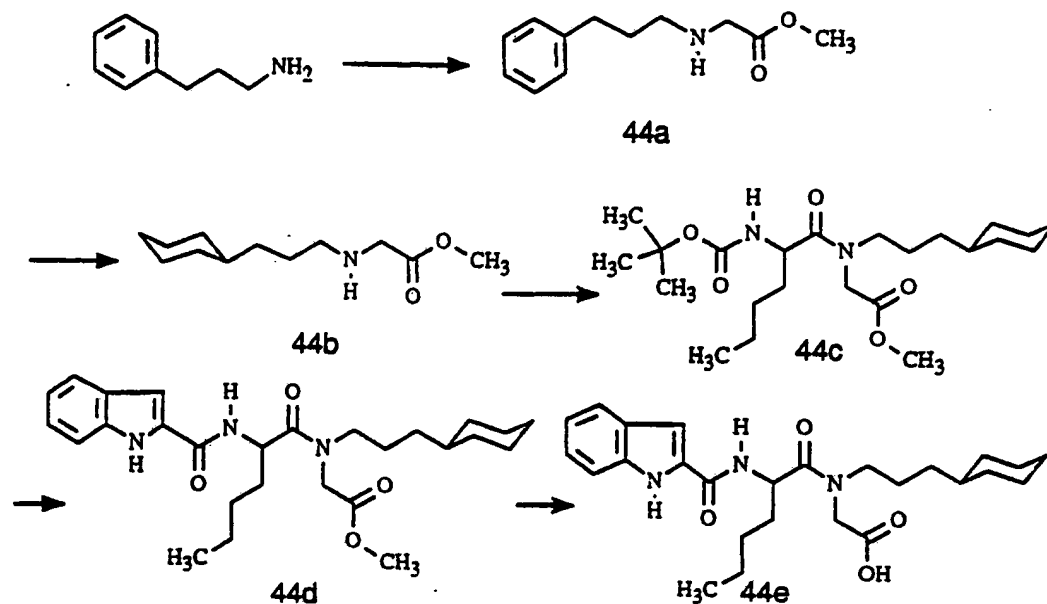
This was prepared from 43e on a 0.50 mmol scale following the method described for 33. The product was isolated in 50% yield (95 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A  $t_R=14.2'$  >98%

AAA Peptide content=79%

Mass spec (FAB)  $m/e=523$   $[M+H]^+$

## EXAMPLE 44



### 44a Methyl N-(3-phenylpropyl)-glycinate.

This was prepared from 3-phenylpropylamine on a 20 mmol scale following the method described for 32a. The product was used without purification assuming a yield of 100%.

### 44b Methyl N-(3-cyclohexylpropyl)-glycinate.

This was prepared from 44a on a 20 mmol scale following the method described for 32b. The product was isolated in a yield of 69% and used without further purification.

$^1H$  NMR  $\delta$  2.50 (2H, t, J=7Hz); 3.34 (2H, s); 3.81 (3H, s)

**44c Methyl N-(3-cyclohexylpropyl)-N-((2S)-2-(tert-butyloxycarbonylamino)-hexanoyl)-glycinate.**

This was prepared from 44b on a 5.8 mmol scale following the method described for 32c. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**44d Methyl N-(3-cyclohexylpropyl)-N-((2S)-2-(2-indolecarbonylamino)-hexanoyl)-glycine.**

This was prepared from 44c on a 0.59 mmol scale following the method described for 38c. The product was isolated in 90% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

$^1\text{H}$  NMR Major rotamer  $\delta$  3.64 (1H,d,J=17Hz); 4.21 (1H,d,J=17Hz); 5.05 (1H,m)

Minor rotamer  $\delta$  3.85 (1H,d,J=17Hz); 4.21 (1H,d,J=17Hz); 4.80 (1H,m)

**44e N-(3-Cyclohexylpropyl)-N-((2S)-2-(2-indolecarbonylamino)-hexanoyl)-glycine.**

This was prepared from 44d on a 0.53 mmol scale following the method described for 1f. The product was isolated in 66% yield (120 mg) after flash chromatography (eluant EtOAc:pet.ether:AcOH 60:40:2 v/v/v).

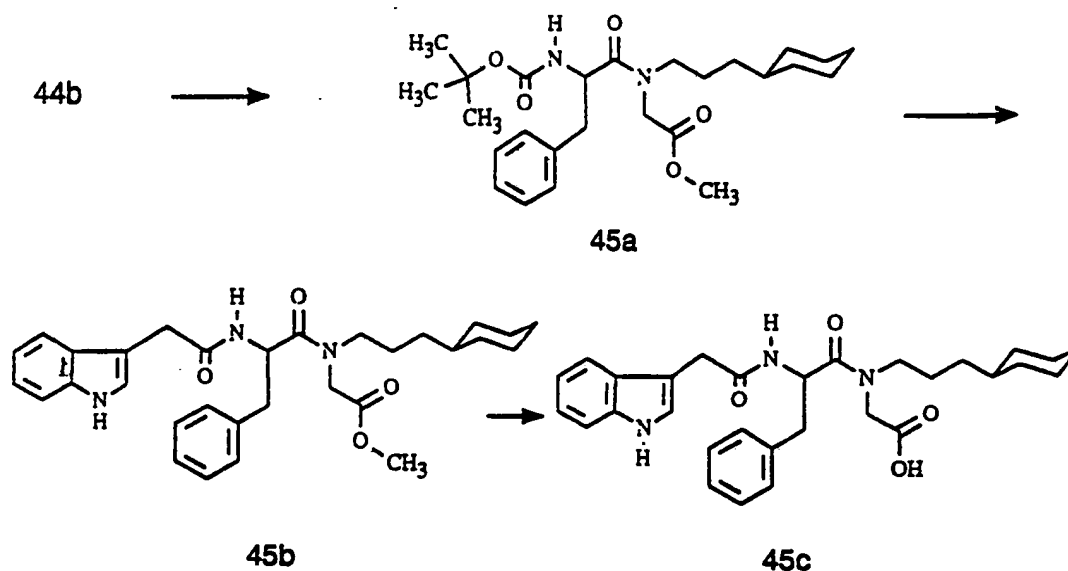
HPLC System A  $t_R$ =16.9' >98%

AAA Peptide content=81%

Mass spec (FAB)  $m/e$ =456  $[\text{M}+\text{H}]^+$



## EXAMPLE 45



**45a** Methyl N-(3-cyclohexylpropyl)-N-(N-(*tert*-butyloxycarbonyl)-phenylalanyl)-glycinate.

This was prepared from 44b on a 2.9 mmol scale following the method described for 32c using BOC-Phe instead of BOC-aminohexanoic acid. The product was isolated in 77% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**45b** Methyl N-(3-cyclohexylpropyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycinate.

This was prepared from 45a on a 2.4 mmol scale following the method described for 38c. The product was isolated in 28% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 70:30 v/v).

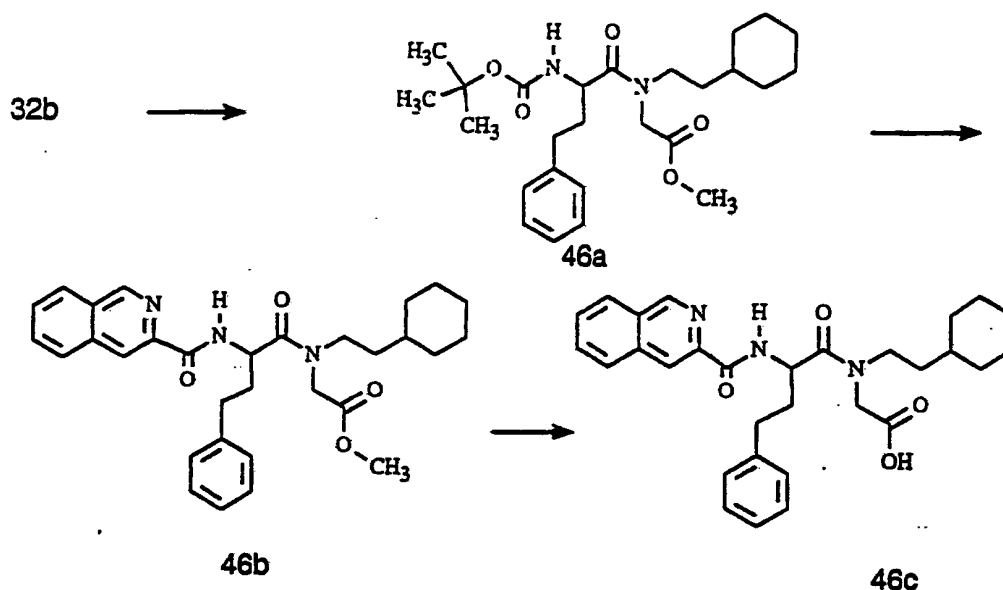
**45c** N-(3-Cyclohexylpropyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycine.

This was prepared from 45b on a 0.68 mmol scale following the method described for 1f. The product was isolated in 46% yield (159 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A  $t_R$ =14.6' >95%

AAA Peptide content=86%

Mass spec (FAB)  $m/e$ =504  $[M+H]^+$

**EXAMPLE 46**

**46a** Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(*tert*-butoxycarbonylamino)-4-phenylbutanoyl)-glycinate.

This was prepared from 32b on a 4.8 mmol scale following the method described for 32c using BOC-amino-4-phenylbutanoic acid instead of BOC-aminohexanoic acid. The product was isolated in 79% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**46b** Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(3-isoquinolinecarboxylamino)-4-phenylbutanoyl)-glycinate.

This was prepared from 46a on a 0.75 mmol scale following the method described for 32c using 3-isoquinolinecarboxylic acid instead of 3-indoleacetic acid. The product was isolated in 62% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**46c** N-(2-Cyclohexylethyl)-N-((2S)-2-(3-isoquinolinecarboxylamino)-4-phenylbutanoyl)-glycine.

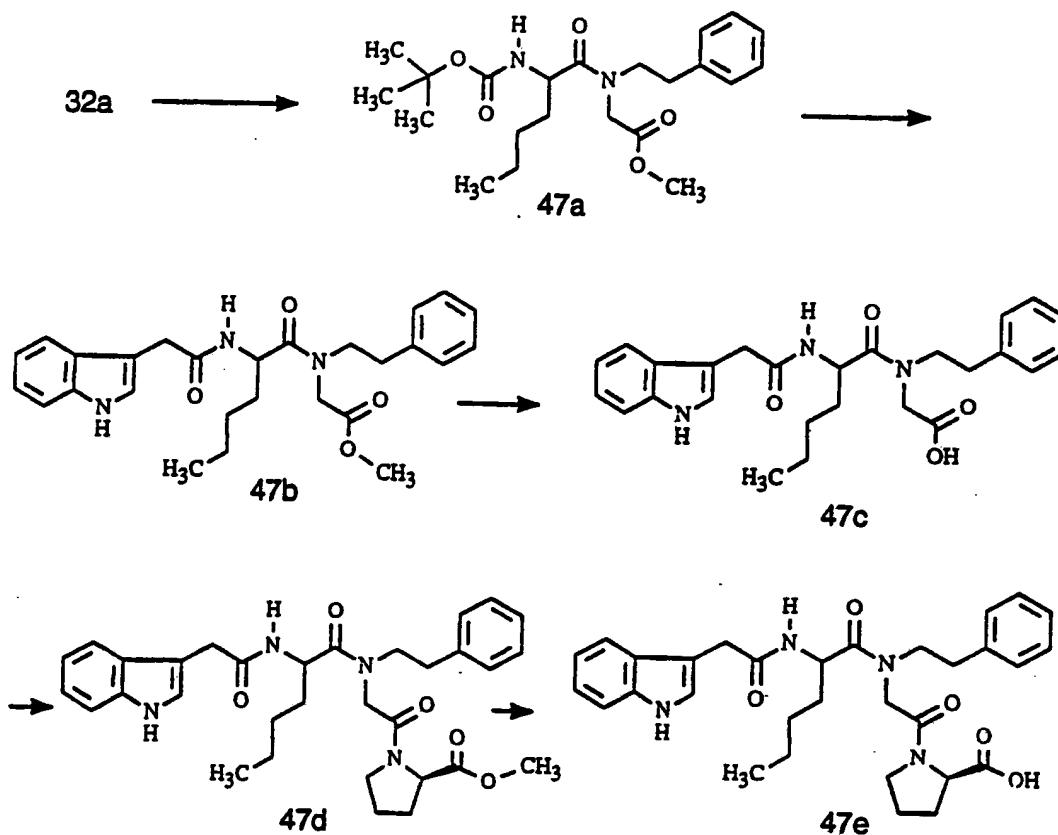
This was prepared from 46b on a 0.47 mmol scale following the method described for 1f. The product was isolated in 52% yield (121 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A  $t_R=17.2'$  >99%

AAA Peptide content=97%

Mass spec (FAB)  $m/e=502$   $[M+H]^+$

### EXAMPLE 47



**47a Methyl N-phenethyl-N-((2S)-2-(*tert*-butoxycarbonylamino)-hexanoyl)-glycinate.**

This was prepared from 32a on a 2.6 mmol scale following the method described for 32c. The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

$R_f$  (EtOAc:hexane 40:60 v/v) 0.35

**47b Methyl N-phenethyl-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycinate.**

This was prepared from 47a on a 1.2 mmol scale following the method described for 32d. The product was isolated in 71% yield after flash chromatography on silica gel (eluant EtOAc:hexane 70:30 v/v).

$R_f$  (EtOAc:hexane 70:30 v/v) 0.16

**47c N-Phenethyl-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycine.**

This was prepared from 47b on a 0.88 mmol scale following the method described for 1f. The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

R<sub>f</sub> (EtOAc:AcOH 100:2 v/v) 0.21

**47d Methyl N-{N-phenethyl-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-prolinate.**

This was prepared from 47c on a 0.22 mmol scale following the method described for 34 using D-ProMe instead of pyrrolidine. The product was isolated in 50% yield after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

R<sub>f</sub> (EtOAc:AcOH 100:2 v/v) 0.16

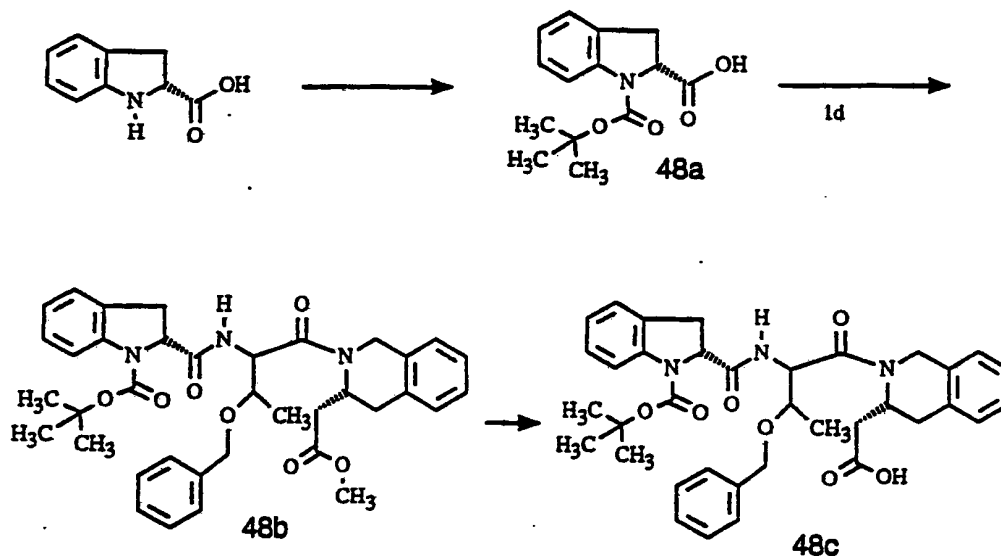
**47e N-{N-Phenethyl-N-((2S)-2-(3-indoleacetyl-amino)-hexanoyl)-glycyl}-D-proline.**

This was prepared from 47d on a 0.11 mmol scale following the method described for 1f. The product was isolated in 38% yield (23 mg) after flash chromatography on silica gel (eluant CHCl<sub>3</sub>:MeOH:AcOH 35:2:1 v/v/v).

HPLC System A t<sub>R</sub>=11.2' >98%

AAA Aha 0.99; Pro 1.01; Peptide content=65%

Mass spec (FAB) m/e=569 [M+H]<sup>+</sup>

**EXAMPLE 48**

**48a 1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from (2R)-2,3-dihydroindole-2-carboxylic acid (M. Vincent *et al.* *Tetrahedron Lett.*, 23, 1677, 1982) on a 65 mmol scale following the method described for 1a. The product was isolated in 98% yield and used without further purification.

**48b Methyl (3R)-2-{N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-O-benzyl-threonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

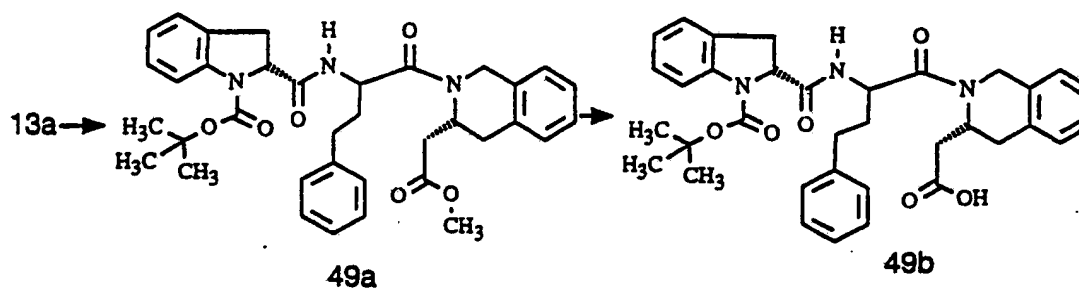
This was prepared from 1d on a 0.68 mmol scale following the method described for 32d using 48a instead of indole-3-acetic acid. The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:1 v/v/v).  $R_f$  (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.36

**48c (3R)-2-{N-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-O-benzyl-threonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 48b on a 0.56 mmol scale following the method described for 1f. The product was isolated in 55% yield (195 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:1 v/v/v).

HPLC System A  $t_R$ =18.0' >98%

Mass spec (FAB)  $m/e$ =628  $[M+H]^+$

**EXAMPLE 49****49a Methyl (3R)-2-((2S)-2-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-4-phenylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 13a on a 0.53 mmol scale following the method described for 48b. The product was isolated in 80% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:2 v/v/v).

**49b** (3R)-2-[(2S)-2-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

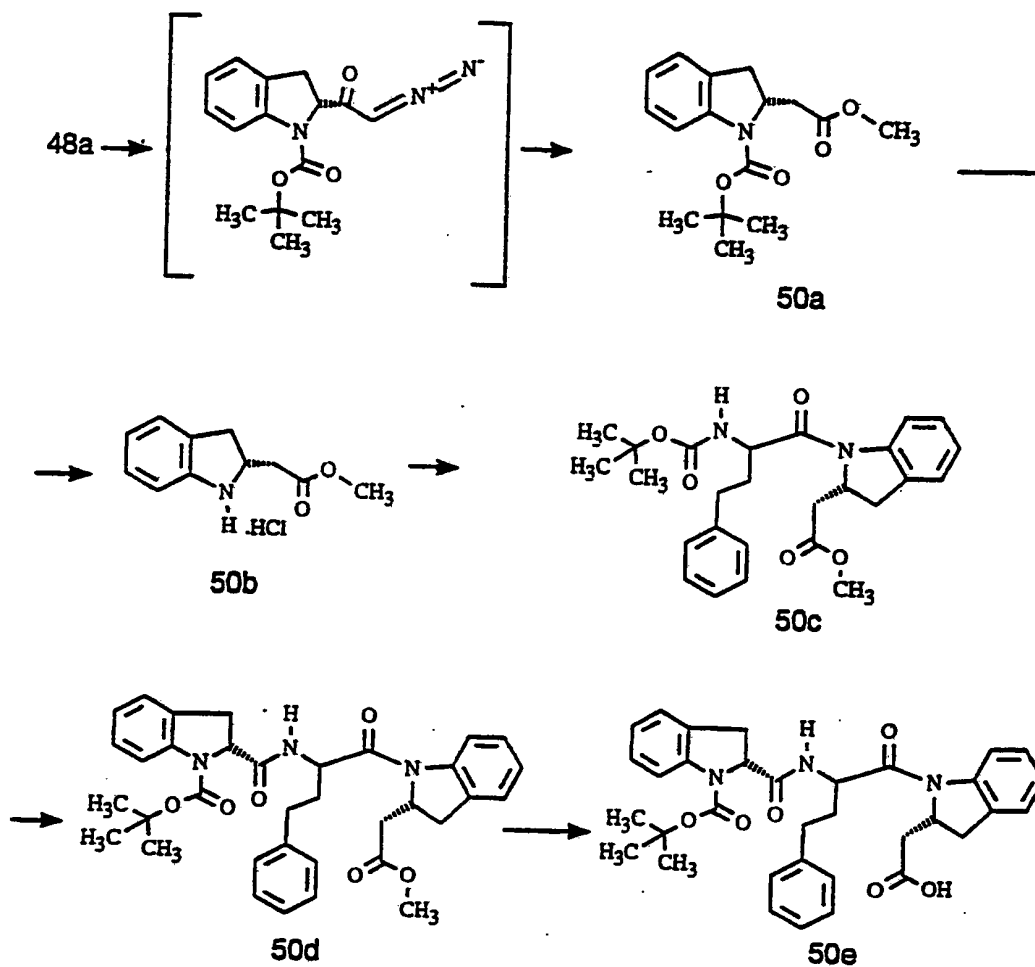
This was prepared from 49a on a 0.21 mmol scale following the method described for 1f. The product was isolated in 53% yield (66 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

HPLC System A  $t_R$ =17.2' >98%

AAA Peptide content=85%

Mass spec (FAB)  $m/e$ =598  $[M+H]^+$

**EXAMPLE 50**



**50a Methyl (2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-acetate.**

This was prepared from 48a on a 55 mmol scale following the method described for 1b. The intermediate diazoketone was purified by flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v), and the product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:hexane 12:88 v/v).

**50b Methyl (2R)-2,3-dihydroindole-2-acetate hydrochloride.**

This was prepared from 50a on a 3 mmol scale following the method described for 1c and was used without purification.

**50c Methyl (2R)-1-[(2S)-2-*tert*-butyloxycarbonylamino-4-phenylbutanoyl]-2,3-dihydroindole-2-acetate.**

This was prepared from 50b on a 3 mmol scale following the method described for 1d using BOC-homophenylalanine instead of N-BOC-O-benzyl-threonine. The product was isolated in 30% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 16:84 v/v).

**50d Methyl (2R)-1-[(2S)-2-[(2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino]-4-phenylbutanoyl]-2,3-dihydroindole-2-acetate.**

This was prepared from 50c on a 0.88 mmol scale following the method described for 48b. The product was isolated in 89% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 30:70:2 v/v/v).

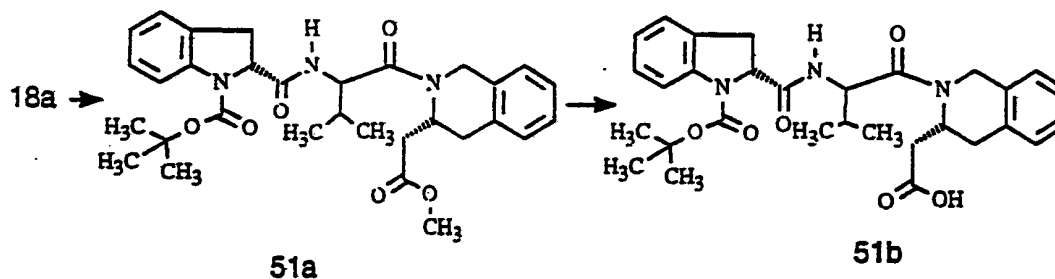
**50e (2R)-1-[(2S)-2-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino]-4-phenylbutanoyl]-2,3-dihydroindole-2-acetic acid.**

This was prepared from 50d on a 0.16 mmol scale following the method described for 1f. The product was isolated in 76% yield (70 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

HPLC System B  $t_R$ =13.5' >95%

AAA Peptide content=92%

Mass spec (FAB)  $m/e$ =584  $[M+H]^+$

**EXAMPLE 51**

**51a** Methyl (3R)-2-(((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 18a on a 0.41 mmol scale following the method described for 48b. The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v then neat EtOAc).

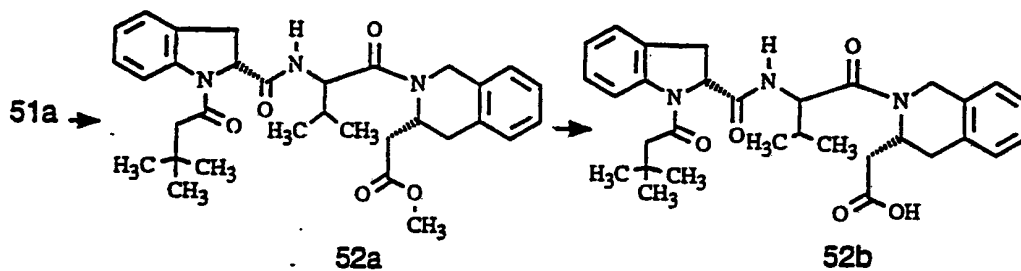
**51b** (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 51a on a 0.29 mmol scale following the method described for 1f. The product was isolated in 70% yield (108 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:1 v/v/v).

HPLC System B  $t_R$ =10.7' >98%

AAA Peptide content=81%

Mass spec (FAB)  $m/e$ =536  $[M+H]^+$

**EXAMPLE 52**



**52a Methyl (3R)-2-(((2R)-1-*tert*-butylacetyl-2,3-dihydroindole-2-carbonyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

A solution of **51a** (198 mg, 0.36 mmol) in 4*N* HCl in dioxan (15 mL) was stirred at room temperature for 30 min., then the solvent was evaporated *in vacuo*, finally with toluene azeotrope. The residue was taken up in CH<sub>2</sub>Cl<sub>2</sub> and cooled to -15°C with stirring. Diisopropylethylamine (0.14 mL, 0.80 mmol) and *tert*-butylacetyl chloride (51 µL, 0.36 mmol) were added and the mixture was stirred at -15°C for 45 min. The solvent was evaporated *in vacuo*, and the residue was partitioned between EtOAc and 0.3*M* KHSO<sub>4</sub>. The organic phase was washed with satd. KHCO<sub>3</sub>, H<sub>2</sub>O and brine, filtered (Whatman<sup>®</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v) to give the title compound (100 mg, 50%).

R<sub>f</sub> (EtOAc:hexane 60:40 v/v) 0.28

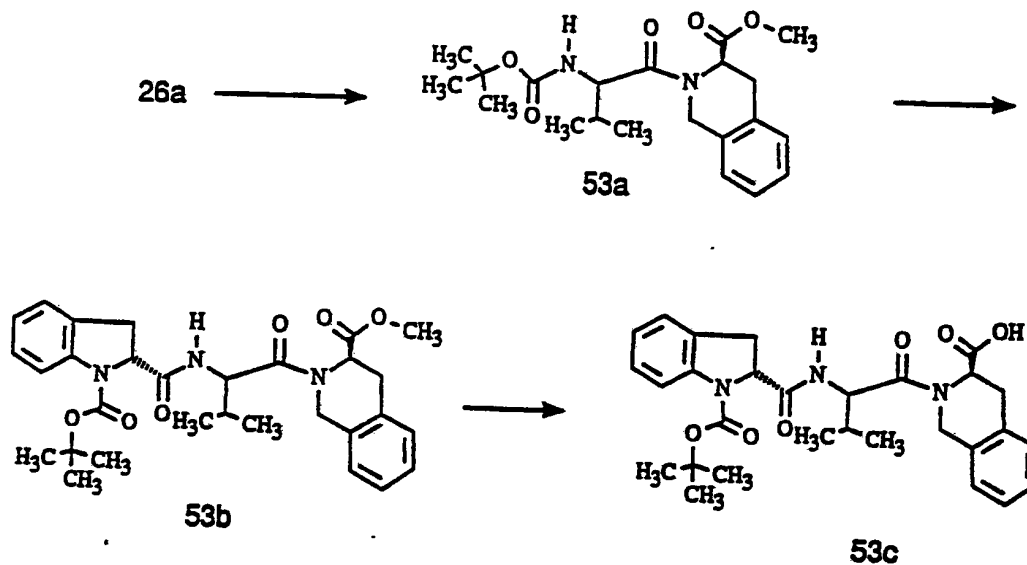
**52b (3R)-2-(((2R)-1-*tert*-Butylacetyl-2,3-dihydroindole-2-carbonyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from **52a** on a 0.18 mmol scale following the method described for **1f**. The product was isolated in 81% yield (78 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:1 v/v/v).

HPLC System A t<sub>R</sub>=14.0' >98%

AAA Peptide content=76%

Mass spec (FAB) m/e=534 [M+H]<sup>+</sup>

**EXAMPLE 53**

**53a** Methyl (3R)-2-(*tert*-butyloxycarbonyl-valyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 26a on a 1.0 mmol scale following the method described for 1d using BOC-valine instead of N-BOC-O-benzyl-threonine. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:hexane 28:72 v/v).  $R_f$  (EtOAc:hexane 25:75 v/v) 0.20

**53b** Methyl (3R)-2-(((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 53a on a 0.68 mmol scale following the method described for 48b. The product was isolated in 81% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:1 v/v/v).  $R_f$  (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.30

**53c** (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

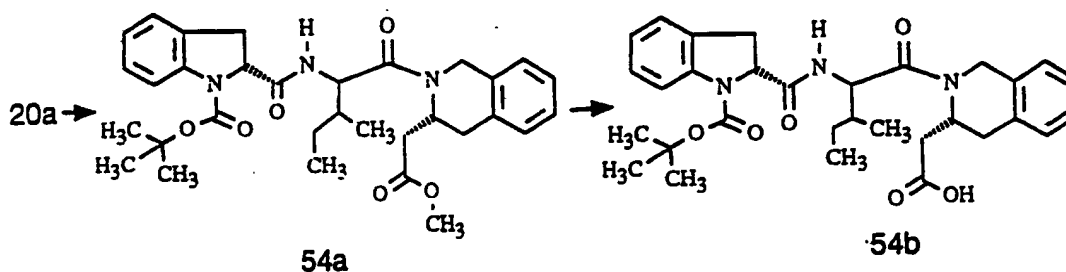
This was prepared from 53b on a 0.52 mmol scale following the method described for 1f. The product was isolated in 50% yield (150 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:1 v/v/v).

HPLC System A  $t_R$ =13.9' >98%

AAA Peptide content=77%

Mass spec (FAB)  $m/e$ =522  $[M+H]^+$

## EXAMPLE 54



**54a** Methyl (3R)-2-(((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-isoleucyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 20a on a 0.16 mmol scale following the method described for 48b. The product was isolated in 94% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

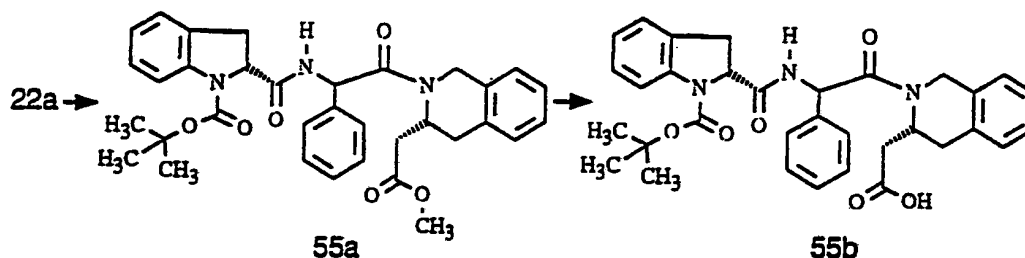
**54b** (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-isoleucyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 54a on a 0.15 mmol scale following the method described for 1f. The product was isolated in 63% yield (55 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R$ =15.3' >98%

AAA Peptide content=66%

Mass spec (FAB)  $m/e$ =550  $[M+H]^+$

**EXAMPLE 55**

**55a** Methyl (3R)-2-[(S)- $\alpha$ -((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carboxylamino)-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 22a on a 0.23 mmol scale following the method described for 48b. The product was isolated in 89% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

**55b** (3R)-2-[(S)- $\alpha$ -((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

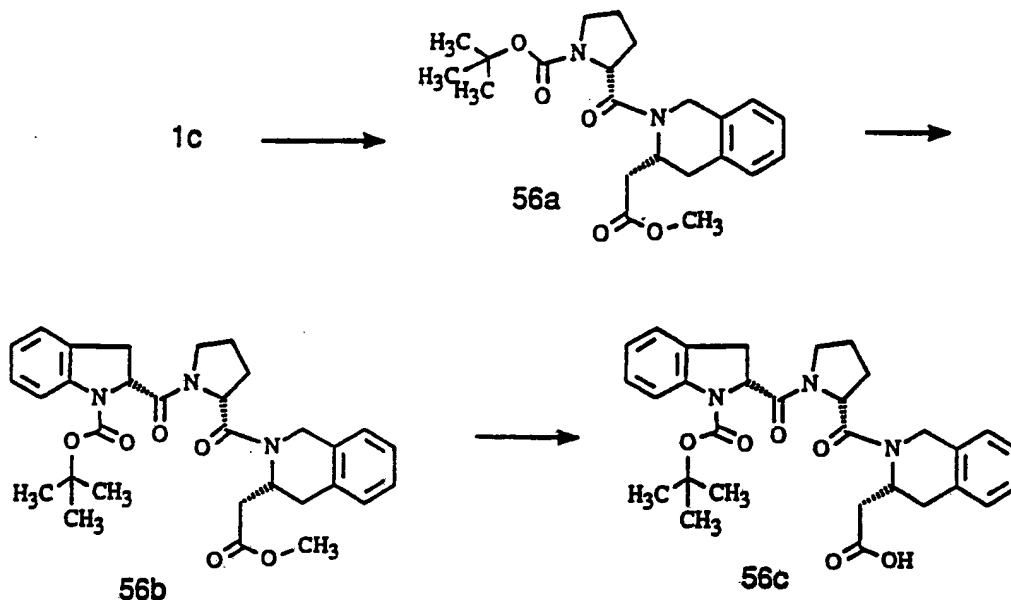
This was prepared from 55a on a 0.21 mmol scale following the method described for 1f. The product was isolated in 66% yield (87 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R$ =15.3' >95%

AAA Peptide content=73%

Mass spec (FAB)  $m/e$ =570 [M+H]<sup>+</sup>

## EXAMPLE 56



**56a Methyl (3R)-2-(*tert*-butoxycarbonyl-D-prolyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 1c on a 1.0 mmol scale following the method described for 1d using BOC-D-proline instead of N-BOC-O-benzyl-threonine. The product was isolated in 74% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

**56b Methyl (3R)-2-(((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-D-prolyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 56a on a 0.37 mmol scale following the method described for 48b. The product was isolated in 87% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:1 v/v/v).

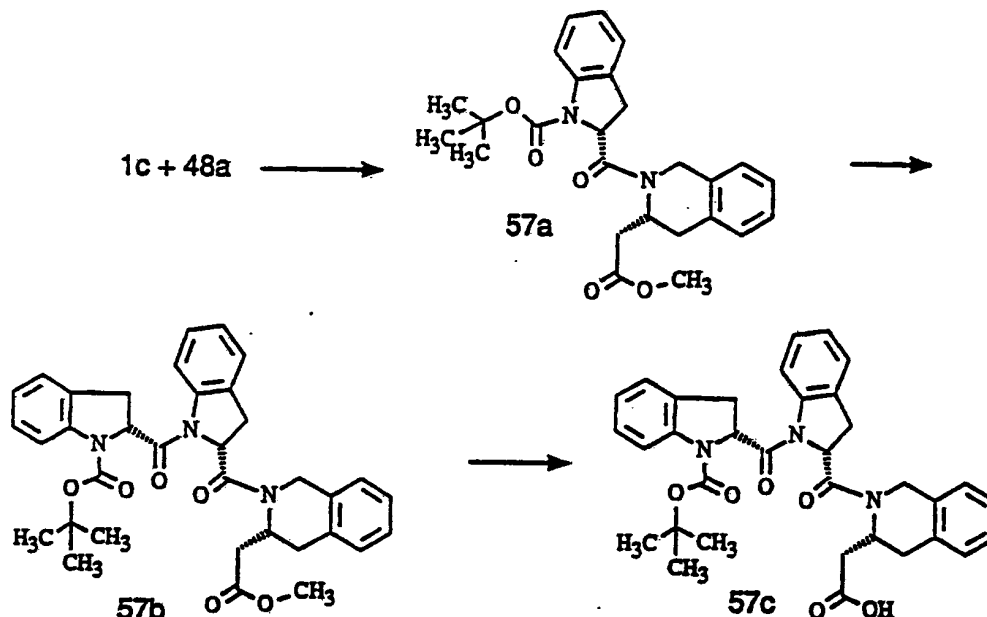
**56c (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-D-prolyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 56b on a 0.32 mmol scale following the method described for 1f. The product was isolated in 39% yield (67 mg) after flash chromatography on silica gel (eluant CHCl<sub>3</sub>:MeOH:AcOH 50:2:1 v/v/v).

HPLC System B  $t_R$ =9.5' >98%

AAA Peptide content=73%

Mass spec (FAB)  $m/e$ =534 [M+H]<sup>+</sup>

**EXAMPLE 57**

**57a** Methyl (3R)-2-((2R)-1-(*tert*-butyloxycarbonyl)-2,3-dihydroindole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c on a 1.13 mmol scale following the method described for 1d using 48a instead of N-BOC-O-benzyl-threonine. The product was isolated in 79% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

**57b** Methyl (3R)-2-((2R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-2,3-dihydroindole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 57a on a 0.90 mmol scale following the method described for 48b. The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

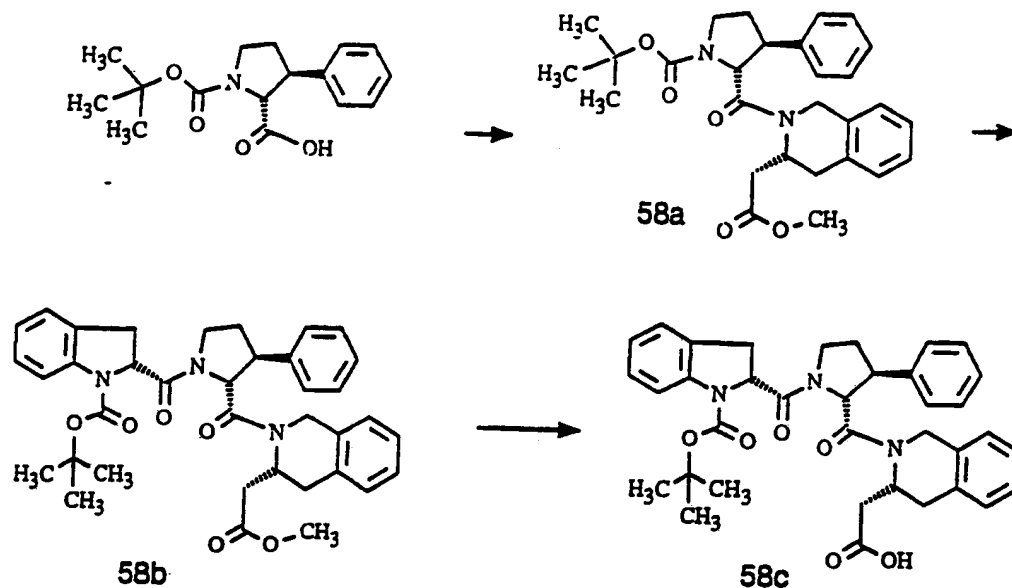
$R_f$  (eluant EtOAc:hexane 60:40 v/v) 0.40

**57c** (3R)-2-((2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-2,3-dihydroindole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 57b on a 0.58 mmol scale following the method described for 1f. The product was isolated in 65% yield (219 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:1 v/v/v).

HPLC System A  $t_R$ =17.7' >99%

Mass spec (FAB)  $m/e$ =582  $[M+H]^+$

**EXAMPLE 58**

**58a Methyl (3R)-2-((2R,3S)-1-*tert*-butyloxycarbonyl-3-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 1c on a 0.17 mmol scale following the method described for 1d using 1-*tert*-butyloxycarbonyl-3-phenyl-pyrrolidine-2-carboxylic acid (J.Y.L. Chung *et al*, *J.Org.Chem.*, 55,270,1990) instead of N-BOC-O-benzyl-threonine. The product was isolated in 75% yield and used without further purification.

$R_f$  (EtOAc:pet. ether 50:50 v/v) 0.18

$^1H$  NMR  $\delta$  1.28, 1.40, 1.48 (9H,3s); 3.59, 3.66 (3H,2s)

**58b Methyl (3R)-2-((2R,3S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-3-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 58a on a 0.098 mmol scale following the method described for 48b. The product was isolated in 78% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:1 v/v/v).

$R_f$  (EtOAc:pet. ether:AcOH 60:40:1 v/v/v) 0.15

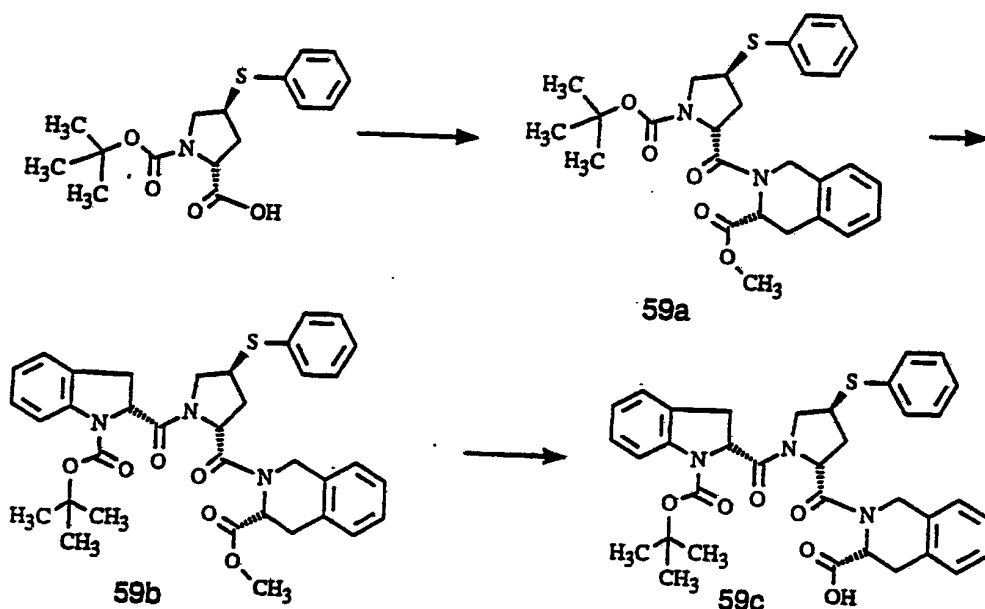
**58c** (3R)-2-((2R,3S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-3-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **58b** on a 0.077 mmol scale following the method described for **1f**. The product was isolated in 83% yield (41 mg) without chromatography.

HPLC System B  $t_R$ =13.9' >99%

Mass spec (FAB)  $m/e$ =610  $[M+H]^+$

### EXAMPLE 59



**59a** Methyl (3R)-2-((2R,4S)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** on a 0.48 mmol scale following the method described for **1d** using (2R,4S)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carboxylic acid (J. Krapcho *et al*, *J. Med. Chem.*, 31,1148,1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 40% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

$R_f$  (EtOAc:hexane 60:40 v/v) 0.43



**59b** Methyl (3R)-2-[(2R,4S)-1-[(2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-4-phenylthio-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 59a on a 0.20 mmol scale following the method described for 48b. The product was isolated in 61% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

$R_f$  (EtOAc:hexane 55:45 v/v) 0.42

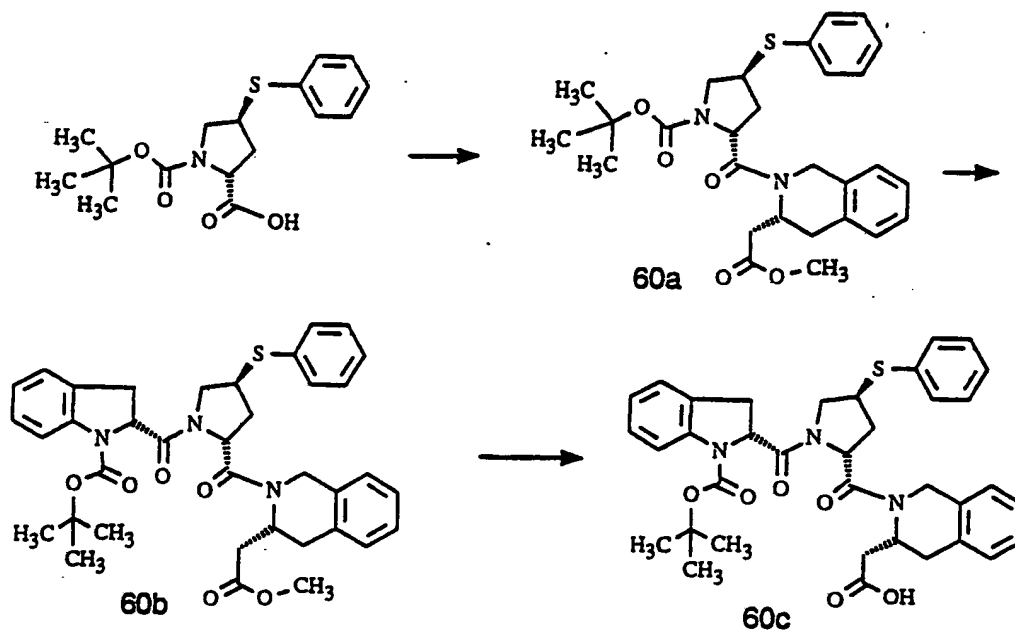
**59c** (3R)-2-[(2R,4S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-4-phenylthio-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 59b on a 0.12 mmol scale following the method described for 1f. The product was isolated in 43% yield (32 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 85:15:1 v/v).

HPLC System A  $t_R$ =20.5' >98%

Mass spec (FAB)  $m/e$ =627  $[M+H]^+$

## EXAMPLE 60



**60a** Methyl (3R)-2-((2R,4S)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c on a 0.48 mmol scale following the method described for 1d using (2R,4S)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carboxylic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 61% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

R<sub>f</sub> (EtOAc:hexane 60:40 v/v) 0.39

**60b** Methyl (3R)-2-((2R,4S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 60a on a 0.29 mmol scale following the method described for 48b. The product was isolated in 77% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v).

R<sub>f</sub> (EtOAc:hexane 60:40 v/v) 0.40

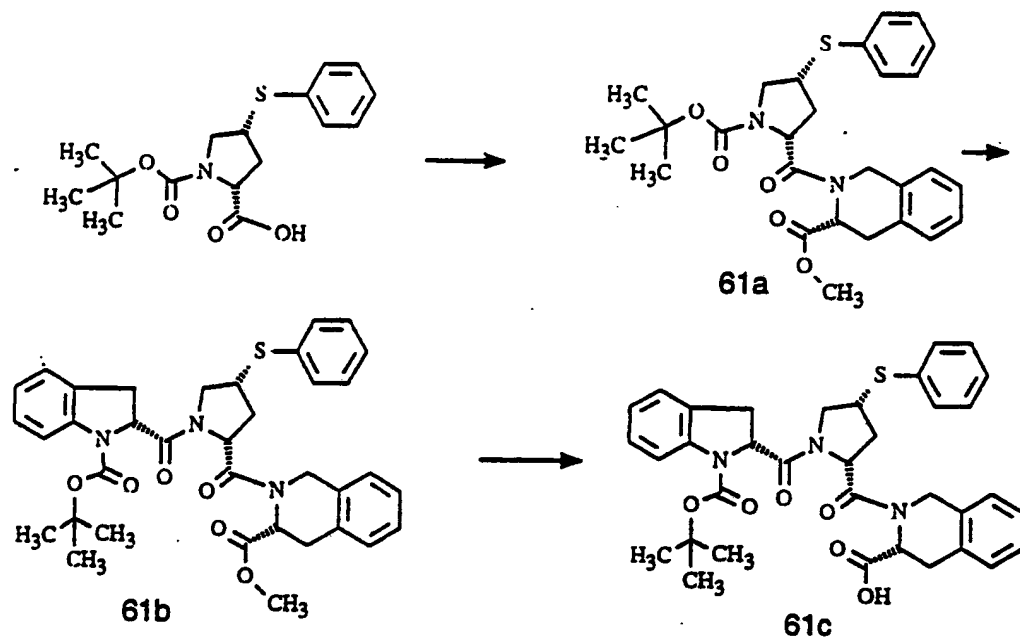
**60c** (3R)-2-((2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 60b on a 0.22 mmol scale following the method described for 1f. The product was isolated in 64% yield (91 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:1 v/v).

HPLC System A t<sub>R</sub>=20.9' >99%

Mass spec (FAB) m/e=642 [M+H]<sup>+</sup>

## EXAMPLE 61



**61a** Methyl (3R)-2-((2R,4R)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 26a on a 0.40 mmol scale following the method described for 1d using (2R,4R)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carboxylic acid (J. Krapcho *et al.*, *J. Med. Chem.*, 31,1148,1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 60% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

**61b** Methyl (3R)-2-((2R,4R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 61a on a 0.24 mmol scale following the method described for 48b. The product was isolated in 48% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

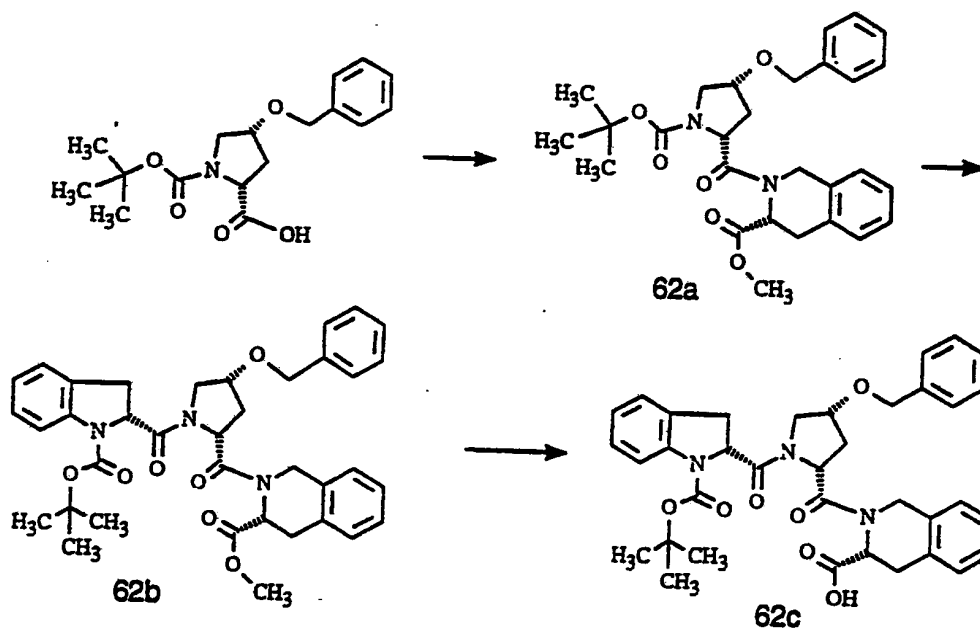
**61c** (3R)-2-[(2R,4R)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-4-phenylthio-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 61b on a 0.12 mmol scale following the method described for 1f. The product was isolated in 69% yield (50 mg) after recrystallization from Et<sub>2</sub>O/hexane.

HPLC System B  $t_R$ =15.0' >98%

Mass spec (FAB)  $m/e$ =628 [M+H]<sup>+</sup>

## EXAMPLE 62



**62a** Methyl (3R)-2-[(2R,4R)-1-*tert*-butyloxycarbonyl-4-benzyloxy-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 26a on a 0.68 mmol scale following the method described for 1d using (2R,4R)-1-*tert*-butyloxycarbonyl-4-benzyloxy-pyrrolidine-2-carboxylic acid (J. Krapcho *et al.*, *J. Med. Chem.*, 31,1148,1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 43% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

$R_f$  (EtOAc:hexane 60:40 v/v) 0.38

62b. Methyl (3R)-2-((2R,4R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyloxy-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 62a on a 0.30 mmol scale following the method described for 48b. The product was isolated in 35% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v).

$R_f$  (EtOAc:hexane 60:40 v/v) 0.36

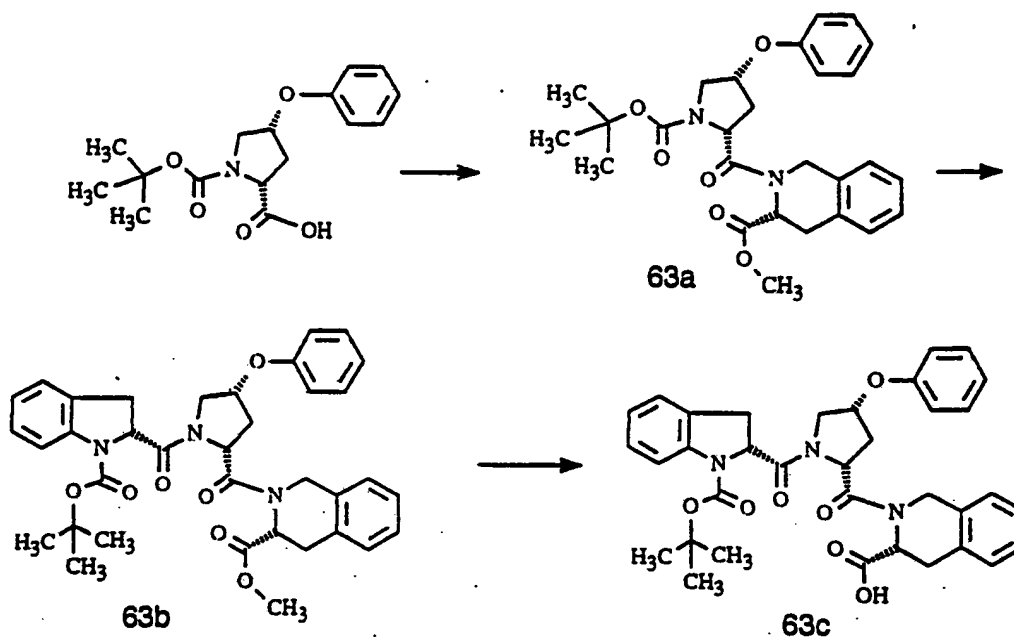
62c (3R)-2-((2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyloxy-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 62b on a 0.11 mmol scale following the method described for 1f. The product was isolated in 29% yield (20 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 90:10:1 v/v).

HPLC System A  $t_R$ =8.8' >98%

Mass spec (FAB)  $m/e$ =626  $[M+H]^+$

### EXAMPLE 63



**63a Methyl (3R)-2-((2R,4R)-1-*tert*-butyloxycarbonyl-4-phenoxy-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 26a on a 0.59 mmol scale following the method described for 1d using (2R,4R)-1-*tert*-butyloxycarbonyl-4-phenoxy-pyrrolidine-2-carboxylic acid (J. Krapcho *et al. J. Med. Chem.*, 31,1148,1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 59% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

**63b Methyl (3R)-2-((2R,4R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenoxy-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 63a on a 0.35 mmol scale following the method described for 48b. The product was isolated in 20% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

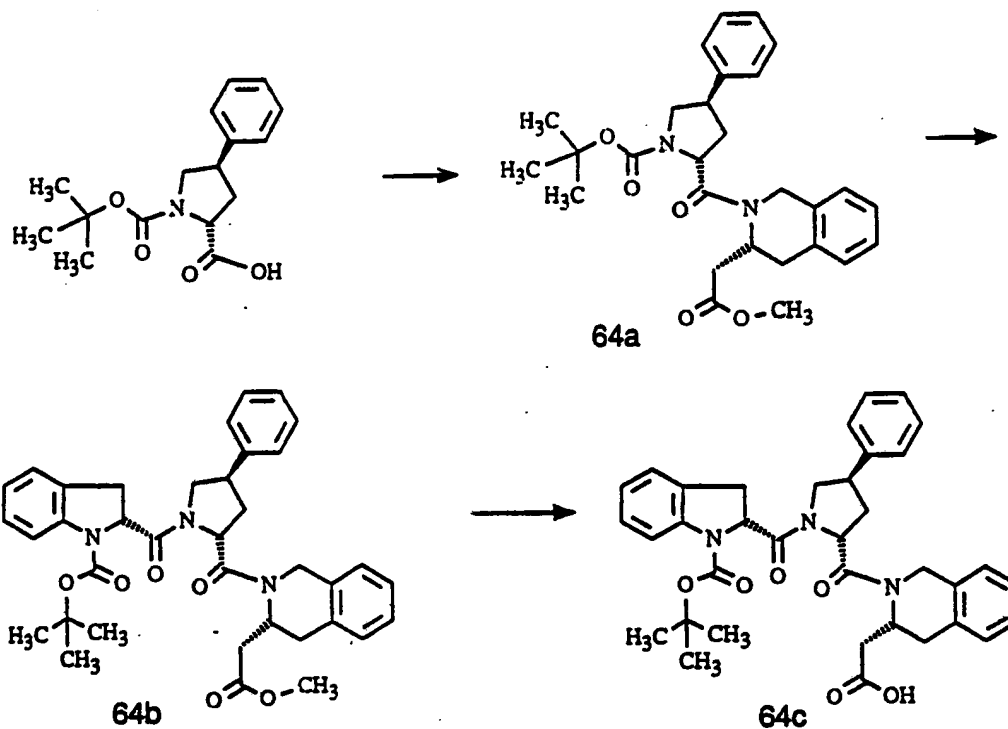
**63c (3R)-2-((2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenoxy-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 63b on a 0.07 mmol scale following the method described for 1f. The product was isolated in 61% yield (26 mg) after recrystallization from MeOH/H<sub>2</sub>O.

HPLC System B  $t_R$ =13.2' >98%

Mass spec (FAB)  $m/e$ =612 [M+H]<sup>+</sup>

## EXAMPLE 64



**64a** Methyl (3R)-2-((2R,4R)-1-tert-butoxycarbonyl-4-phenylpyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c on a 0.24 mmol scale following the method described for 1d using (2R,4S)-1-tert-butoxycarbonyl-4-phenylpyrrolidine-2-carboxylic acid (J. Krapcho *et al*, *J. Med. Chem.*, 31, 1148, 1988) instead of N-BOC-O-benzyl-threonine. The product was used without further purification assuming a yield of 100%.

$R_f$  (EtOAc:pet. ether 30:70 v/v) 0.11

**64b** Methyl (3R)-2-((2R,4R)-1-((2R)-1-tert-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylpyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 64a on a 0.24 mmol scale following the method described for 48b. The product was isolated in 33% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:1 v/v/v).

$R_f$  (EtOAc:pet. ether:AcOH 40:60:1) 0.09

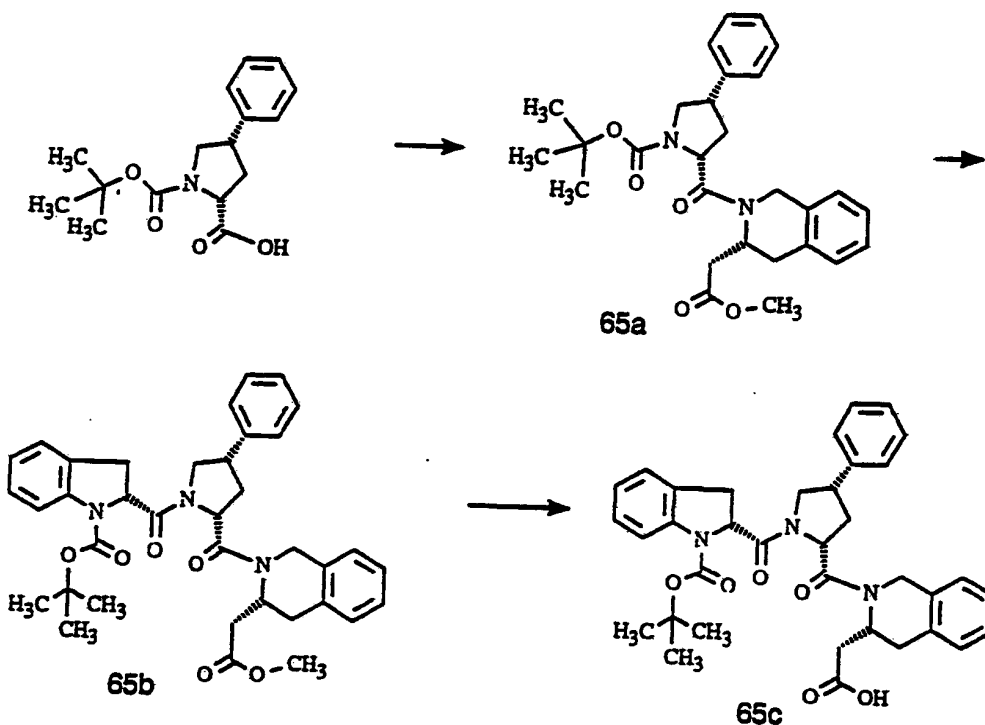
**64c** (3R)-2-[(2R,4R)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-4-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **64b** on a 0.08 mmol scale following the method described for **1f**. The product was isolated in 100% yield (54 mg) without chromatography.

HPLC System B  $t_R$ =15.4' >98%

Mass spec (FAB)  $m/e$ =610  $[M+H]^+$

### EXAMPLE 65



**65a** Methyl. (3R)-2-[(2R,4S)-1-*tert*-butyloxycarbonyl-4-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** on a 0.24 mmol scale following the method described for **1d** using (2R,4R)-1-*tert*-butyloxycarbonyl-4-phenyl-pyrrolidine-2-carboxylic acid (J. Krapcho *et al.*, *J. Med. Chem.*, 31,1148,1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 78% yield and used without further purification.

$R_f$  (EtOAc:pet. ether 30:70 v/v) 0.11



**65b** Methyl (3R)-2-((2R,4S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 65a on a 0.31 mmol scale following the method described for 48b. The product was isolated in 74% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:1 v/v/v).

$R_f$  (EtOAc:pet. ether:AcOH 25:85:1) 0.10

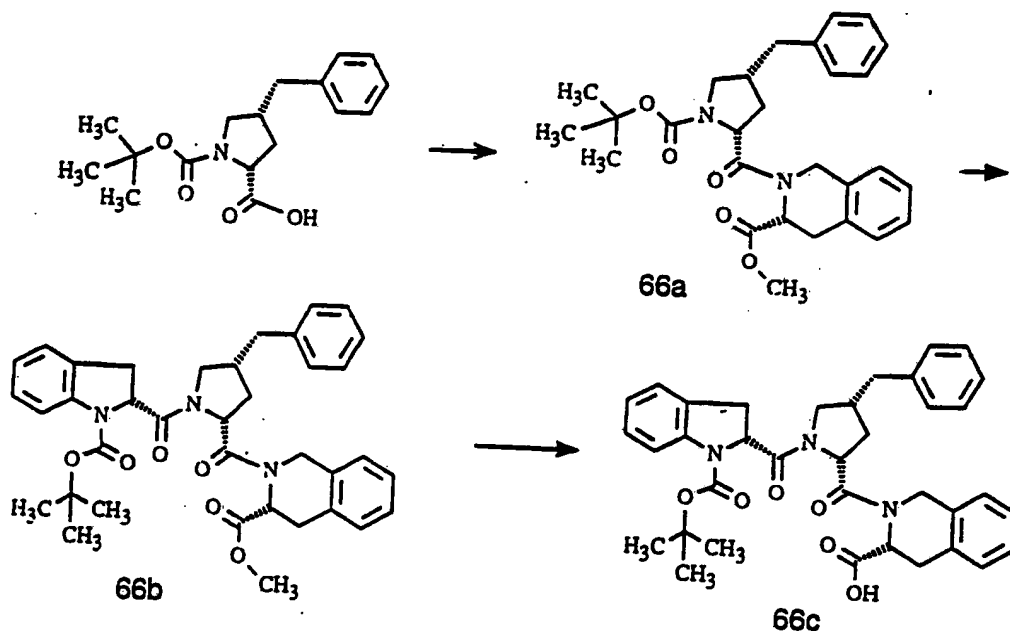
**65c** (3R)-2-((2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 65b on a 0.30 mmol scale following the method described for 1f. The product was isolated in 79% yield (149 mg) without chromatography.

HPLC System B  $t_R$ =14.8' >95%

Mass spec (FAB)  $m/e$ =610  $[M+H]^+$

## EXAMPLE 66



**66a. Methyl (3R)-2-((2R,4S)-1-*tert*-butyloxycarbonyl-4-benzyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 26a on a 0.66 mmol scale following the method described for 1d using (2R,4S)-1-*tert*-butyloxycarbonyl-4-benzyl-pyrrolidine-2-carboxylic acid (J. Krapcho *et al.*, *J. Med. Chem.*, 31, 1148, 1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 55% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:1 v/v/v).

**66b Methyl (3R)-2-((2R,4S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

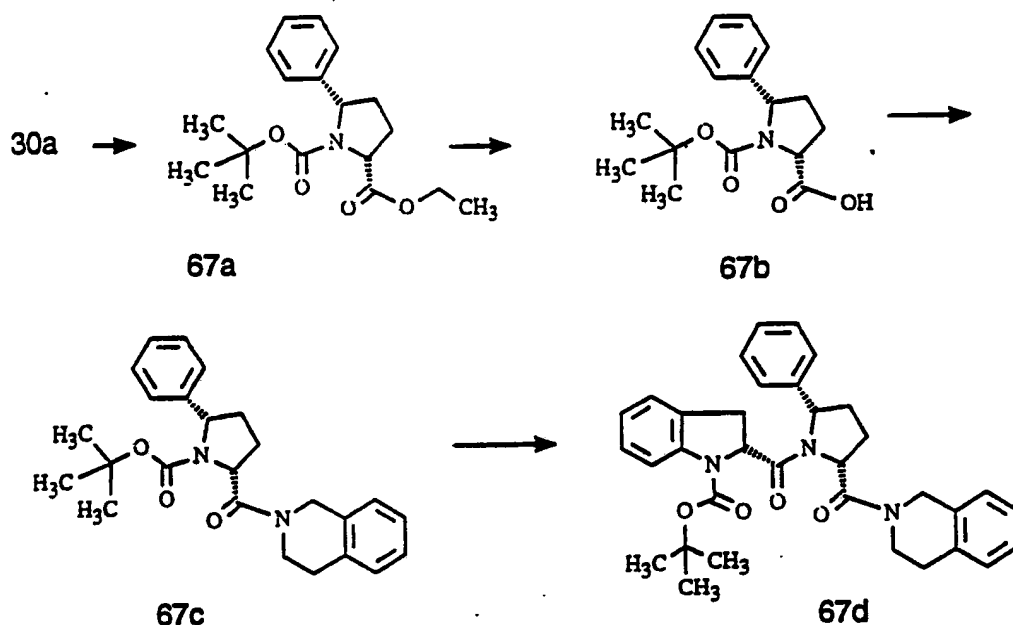
This was prepared from 66a on a 0.35 mmol scale following the method described for 48b. The product was isolated in 33% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:1 v/v/v).

**66c (3R)-2-((2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 66b on a 0.11 mmol scale following the method described for 1f. The product was isolated in 63% yield (43 mg) after recrystallization from MeOH/H<sub>2</sub>O.

HPLC System B  $t_R$ =14.6' >95%

Mass spec (FAB)  $m/e$ =610 [M+H]<sup>+</sup>

**EXAMPLE 67****67a Ethyl (2R,5S)-1-tert-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carboxylate.**

To a solution of 30a (290 mg, 1.32 mmol) in  $CH_2Cl_2$  (10 mL) was added di-*tert*-butyl pyrocarbonate (576 mg, 2.64 mmol), and the mixture was stirred at room temperature for 3 hrs. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 15:85) to give the title compound (400 mg, 95%).

$R_f$  (EtOAc:pet. ether 15:85) 0.35

**67b (2R,5S)-1-tert-Butyloxycarbonyl-5-phenyl-pyrrolidine-2-carboxylic acid.**

This was prepared from 67a on a 1.25 mmol scale following the method described for 1f. The product was isolated in 93% yield and used without further purification.

**67c 2-((2R,5S)-1-tert-Butyloxycarbonyl-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline.**

This was prepared from 67b and tetrahydroisoquinoline on a 0.38 mmol scale following the method described for 1d. The product was isolated in 74% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

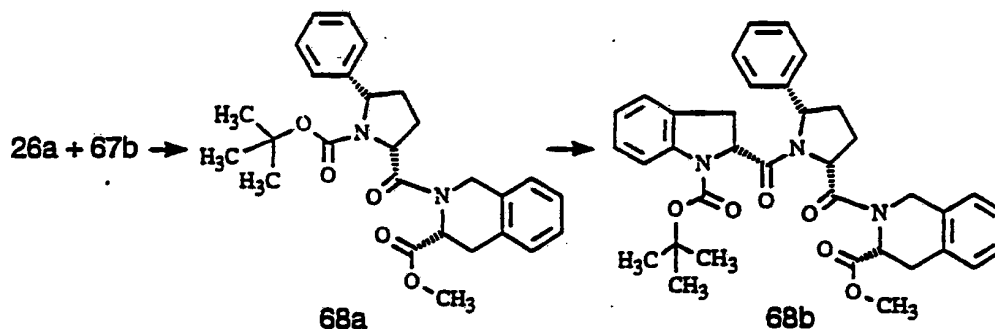
**67d** 2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline.

This was prepared from 67c on a 0.28 mmol scale following the method described for 48b. The product was isolated in 64% yield (98 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

HPLC System A  $t_R$ =25.0' >99%

Mass spec (FAB)  $m/e$ =552 [M+H]<sup>+</sup>

## EXAMPLE 68



**68a** Methyl (3R)-2-((2R,5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 67b and 26a on a 0.27 mmol scale following the method described for 1d. The product was isolated in 56% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

<sup>1</sup>H NMR  $\delta$  1.13 (9H,s); 3.63 (3H,s); 5.69 (1H,t, J=4Hz)

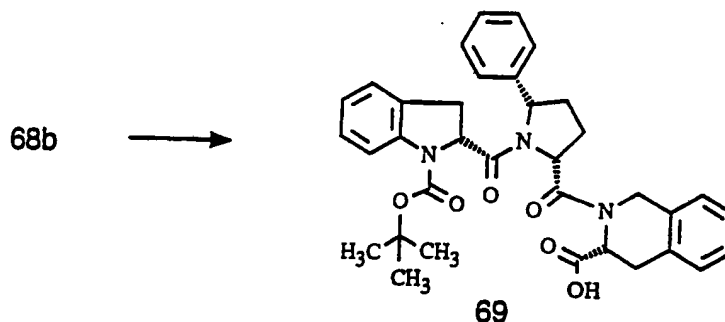
**68b** Methyl (3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 68a on a 1.0 mmol scale following the method described for 48b. The product was isolated in 68% yield (415 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

HPLC System A  $t_R$ =24.7' >99%

Mass spec (FAB)  $m/e$ =610 [M+H]<sup>+</sup>

## EXAMPLE 69



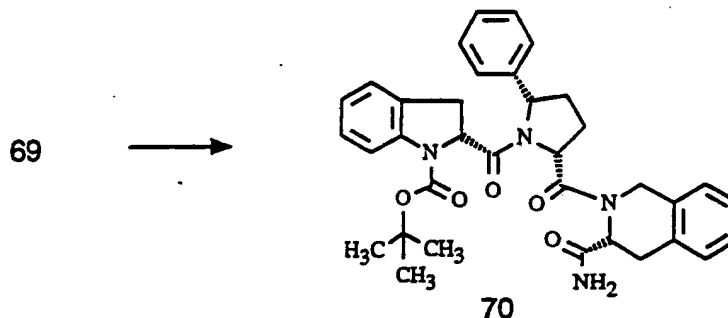
**69 (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 68b on a 0.13 mmol scale following the method described for 1f. The product was isolated in 50% yield (38 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A  $t_R$ =14.9' >98%

Mass spec (FAB)  $m/e$ =618  $[M+Na]^+$

## EXAMPLE 70



**70 (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxamide.**

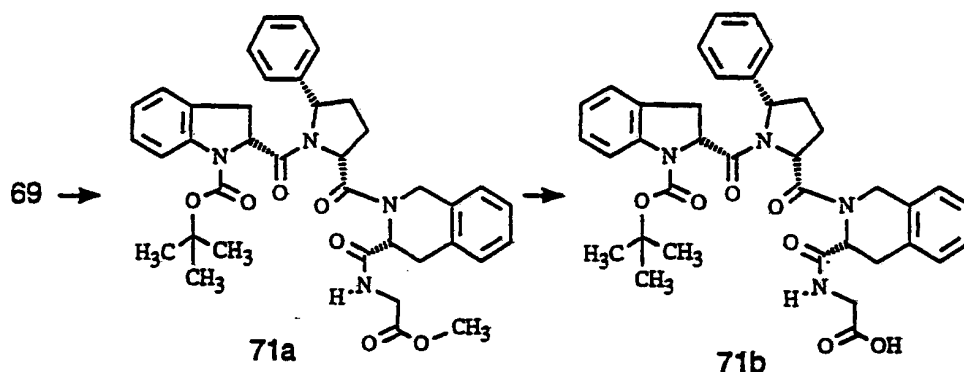
To an ice-cold stirred solution of 69 (107 mg, 0.18 mmol) and pentafluorophenol (37 mg, 0.2 mmol) in  $CH_2Cl_2$  (10 mL) was added WSCD.HCl (478 mg, 0.4 mmol). The mixture was stirred at 0°C for 1 hr., then c. aqueous  $NH_3$  (0.5 mL) was added and vigorous stirring was continued for 3 hr. The mixture was partitioned between EtOAc and  $H_2O$ , and the organic phase was washed with 10%  $KHSO_4$ , satd.  $KHCO_3$  and brine, filtered (Whatman<sup>®</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was

purified by flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v) to give the title compound (87 mg, 81%).

HPLC System A  $t_R$ =20.1' >99%

Mass spec (FAB)  $m/e$ =595  $[M+H]^+$

## EXAMPLE 71



**71a** Methyl N-((3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-glycinate.

This was prepared from 69 on a 0.30 mmol scale following the method described for 38b. The product was isolated in 85% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 65:35 v/v).

**71b** N-((3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-glycine.

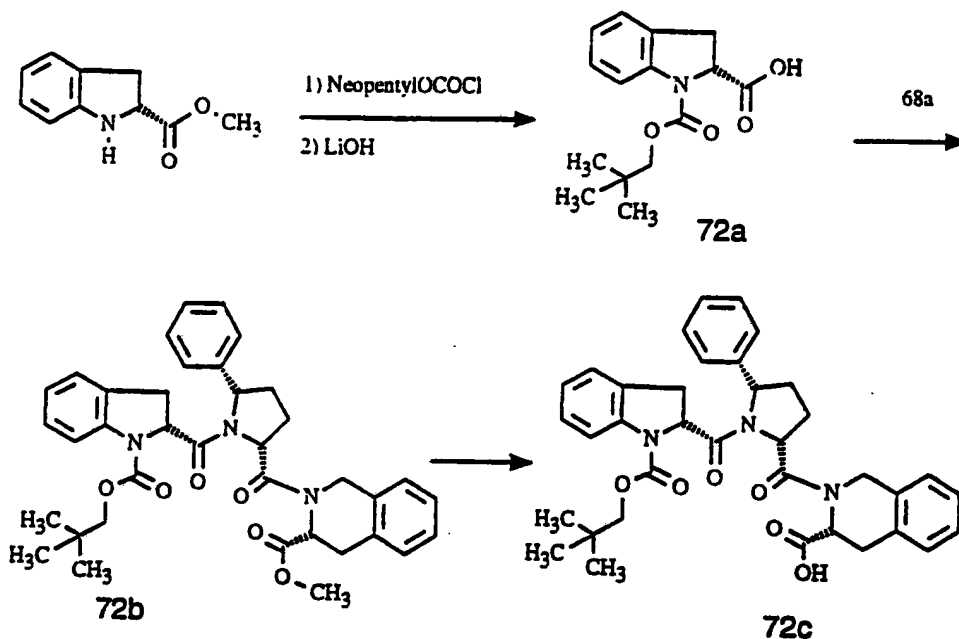
This was prepared from 71a on a 0.26 mmol scale following the method described for 1f. The product was isolated in 71% yield (120 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A  $t_R$ =18.4' >99%

AAA Peptide content=76%

Mass spec (FAB)  $m/e$ =653  $[M+H]^+$

## EXAMPLE 72

**72a (2R)-1-Neopentylloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

To an ice-cold stirred solution of neopentyl alcohol (88mg, 1 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 mL) was added triphosgene (110 mg, 0.37 mmol) and pyridine (84  $\mu\text{L}$ , 1.02 mmol). The mixture was allowed to warm to room temperature and stirred for 1 hr. then cooled to  $0^\circ\text{C}$ . A solution of methyl (2R)-2,3-dihydroindole-2-carboxylate hydrochloride (107 mg, 0.5 mmol) and diisopropylethylamine (90  $\mu\text{L}$ , 0.45 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added and the mixture was stirred at room temperature for 3 hr. The solvent was removed *in vacuo* and the residue was taken up in EtOAc. The solution was washed with 1M HCl (x3) and brine, filtered (Whatman<sup>R</sup> IPS phase separator), and concentrated *in vacuo*. The residue was taken up in dioxan (10 mL) and a solution of LiOH (24 mg, 1 mmol) in  $\text{H}_2\text{O}$  (2 mL) was added. The mixture was stirred at room temperature for 90 min., then the solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc and 10% aq.  $\text{KHSO}_4$ . The organic phase was washed with brine, filtered (Whatman<sup>R</sup> IPS phase separator), and concentrated *in vacuo* to give the title compound (90 mg, 62%) which was used without further purification.

**72b Methyl (3R)-2-((2R,5S)-1-((2R)-1-neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 68a and 72a on a 0.29 mmol scale following the method described for 48b. The product was isolated in 50% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

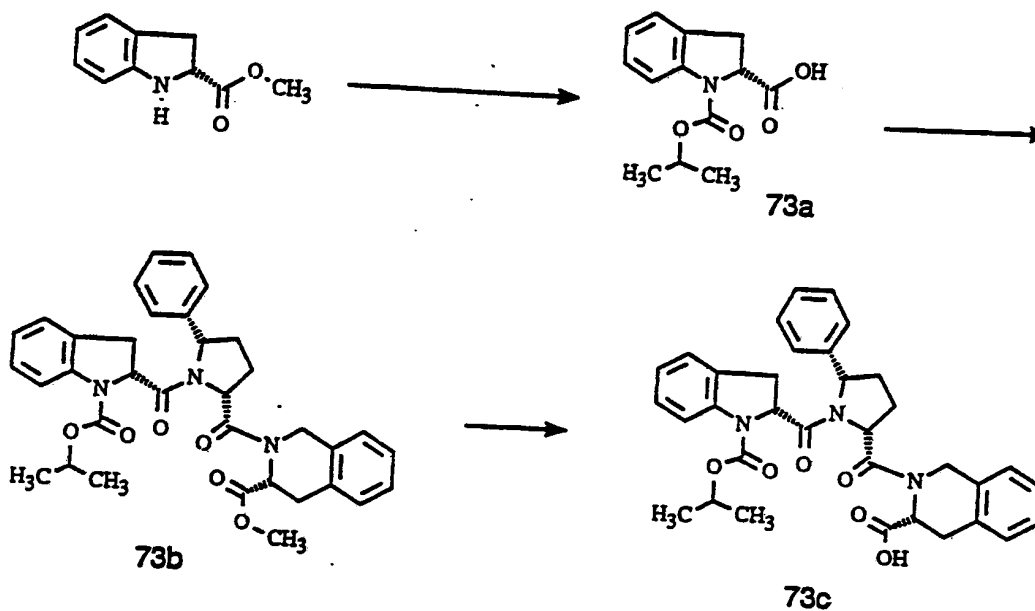
**72c (3R)-2-((2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 72b on a 0.14 mmol scale following the method described for 1f. The product was isolated in 81% yield (69 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A  $t_R=22.4'$  >95%

Mass spec (FAB)  $m/e=610$   $[M+H]^+$

### EXAMPLE 73





**73a (2R)-1-Isopropoxyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from isopropanol on a 0.5 mmol scale following the method described for 72a. The product was isolated in 80% yield and used without further purification.

**73b Methyl (3R)-2-((2R,5S)-1-((2R)-1-isopropoxyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

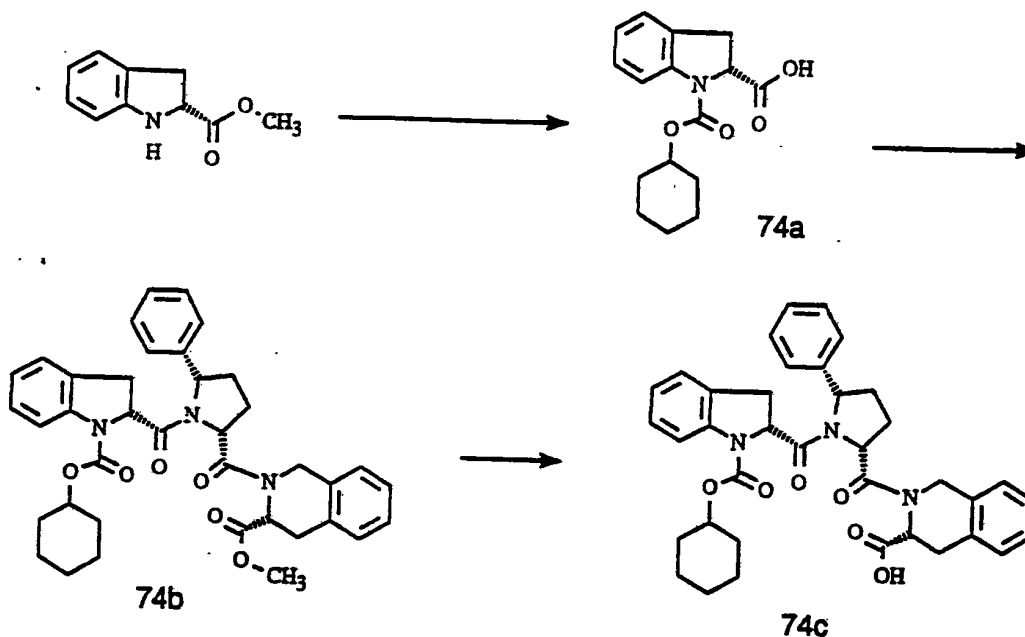
This was prepared from 68a and 73a on a 0.33 mmol scale following the method described for 48b. The product was isolated in 59% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 45:55 v/v).

**73c (3R)-2-((2R,5S)-1-((2R)-1-Isopropoxyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 73b on a 0.19 mmol scale following the method described for 1f. The product was isolated in 63% yield (70 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A  $t_R$ =18.5' >90%

Mass spec (FAB)  $m/e$ =582  $[M+H]^+$

**EXAMPLE 74****74a (2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from cyclohexanol on a 0.5 mmol scale following the method described for 72a. The product was isolated in 72% yield and used without further purification.

**74b Methyl (3R)-2-((2R,5S)-1-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 68a and 74a on a 0.27 mmol scale following the method described for 48b. The product was isolated in 73% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

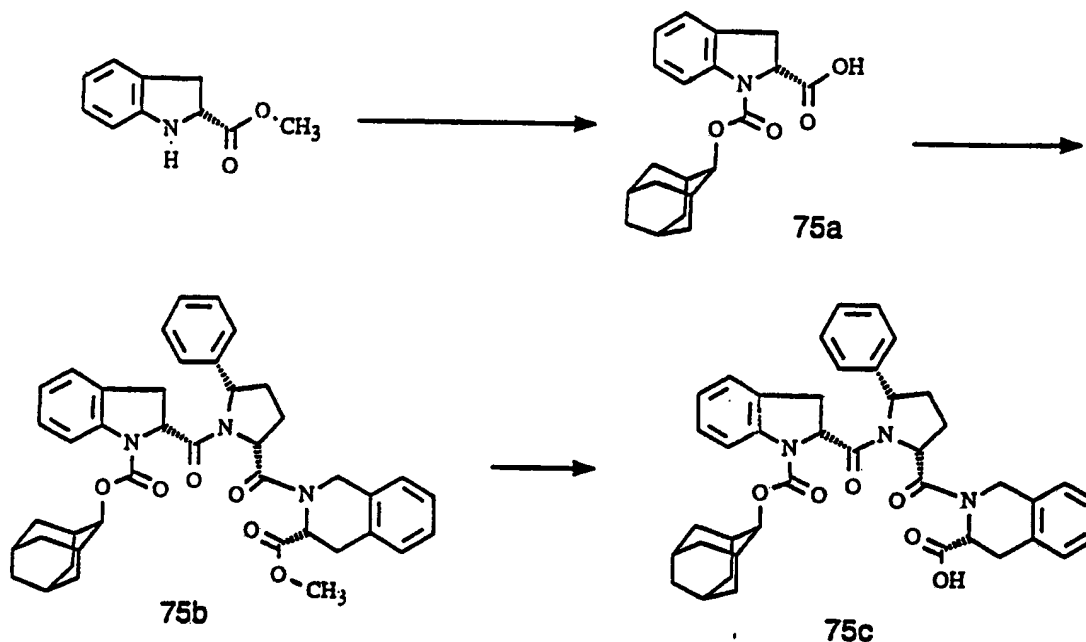
**74c (3R)-2-((2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 74b on a 0.20 mmol scale following the method described for 1f. The product was isolated in 84% yield (104 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A  $t_R=23.0'$  >95%

Mass spec (FAB)  $m/e=621$   $[M+H]^+$

### EXAMPLE 75



**75a (2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from 2-adamantanol on a 0.5 mmol scale following the method described for 72a. The product was isolated in 80% yield and used without further purification.

**75b Methyl (3R)-2-((2R,5S)-1-((2R)-1-(2-adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 68a and 75a on a 0.33 mmol scale following the method described for 48b. The product was isolated in 29% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

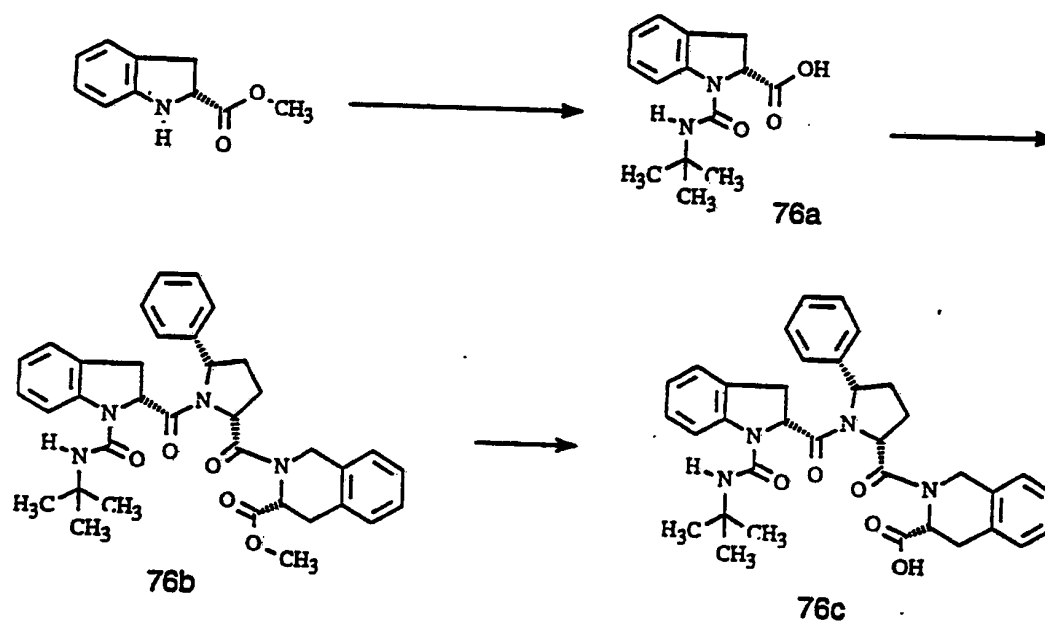
**75c** (3R)-2-[(2R,5S)-1-[(2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 75b on a 0.09 mmol scale following the method described for 1f. The product was isolated in 81% yield (49 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A  $t_R$ =27.9' >98%

Mass spec (FAB)  $m/e$ =674 [M+H]<sup>+</sup>

## EXAMPLE 76



**76a** (2R)-1-*tert*-Butylcarbamoyl-2,3-dihydroindole-2-carboxylic acid.

To an ice-cold stirred solution of methyl (2R)-2,3-dihydroindole-2-carboxylate hydrochloride (107 mg, 0.5 mmol) and diisopropylethylamine (110  $\mu$ L, 0.6 mmol) in  $\text{CH}_2\text{Cl}_2$  (2 mL) was added *tert*-butylisocyanate (120 mg, 1.2 mmol). The mixture was allowed to warm to room temperature and stirred for 6 days then the solvent was removed *in vacuo* and the residue was taken up in EtOAc. The solution was washed with 1M HCl (x3) and brine, filtered (Whatman<sup>®</sup> IPS phase separator), and concentrated *in vacuo*. The residue was taken up in dioxan (10 mL) and a solution of LiOH (24 mg, 1 mmol) in  $\text{H}_2\text{O}$

(2 mL) was added. The mixture was stirred at room temperature for 90 min., then the solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc and 10% aq. KHSO<sub>4</sub>. The organic phase was washed with brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and concentrated *in vacuo* to give the title compound (120 mg, 91%) which was used without further purification.

**76b Methyl (3R)-2-((2R,5S)-1-((2R)-1-*tert*-butylcarbamoyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 68a and 76a on a 0.37 mmol scale following the method described for 48b. The product was isolated in 13% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

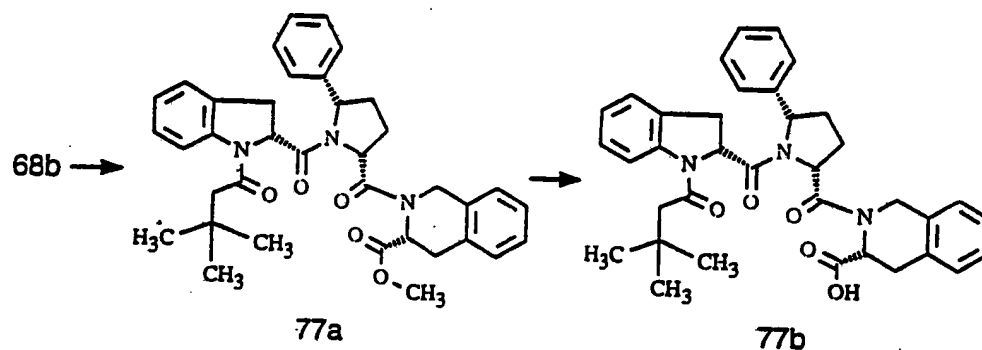
**76c (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butylcarbamoyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 76b on a 0.05 mmol scale following the method described for 1f. The product was isolated in 67% yield (20 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 75:25:2 v/v/v).

HPLC System A  $t_R=12.2'$  >98%

Mass spec (FAB)  $m/e=595$  [M+H]<sup>+</sup>

## EXAMPLE 77



**77a** Methyl (3R)-2-((2R,5S)-1-((2R)-1-*tert*-butylacetyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 68b on a 0.18 mmol scale following the method described for 52a. The product was isolated in 81% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

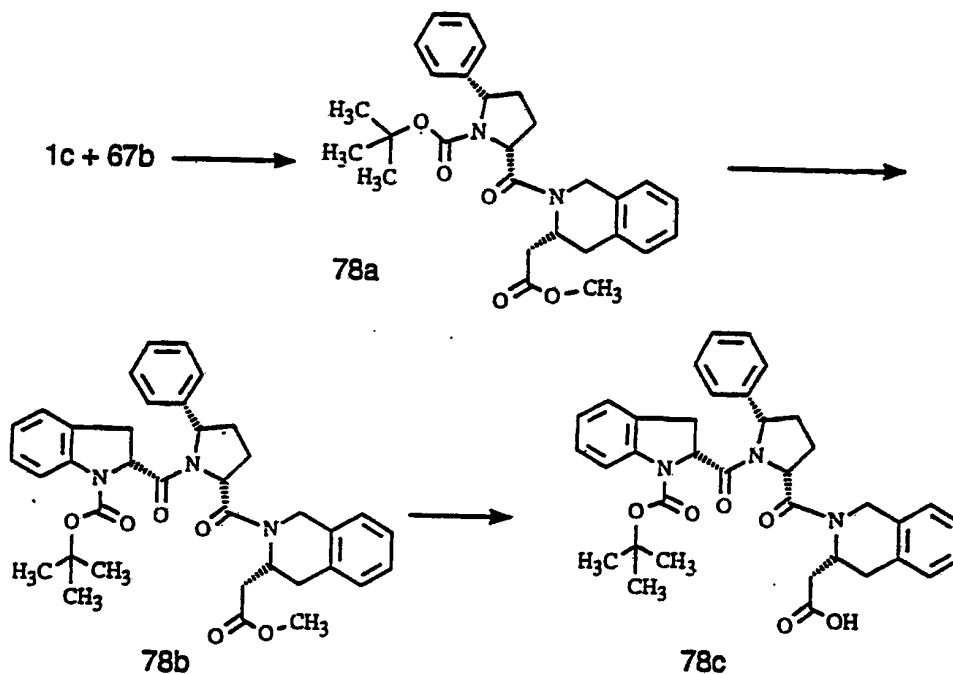
**77b** (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butylacetyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 77a on a 0.14 mmol scale following the method described for 1f. The product was isolated in 82% yield (68 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A  $t_R$ =20.0' >99%

Mass spec (FAB)  $m/e$ =594  $[M+H]^+$

## EXAMPLE 78



**78a Methyl (3R)-2-((2R,5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 1c and 67b on a 0.58 mmol scale following the method described for 1d. The product was isolated in 87% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**78b Methyl (3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 78a on a 0.36 mmol scale following the method described for 48b. The product was isolated in 98% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

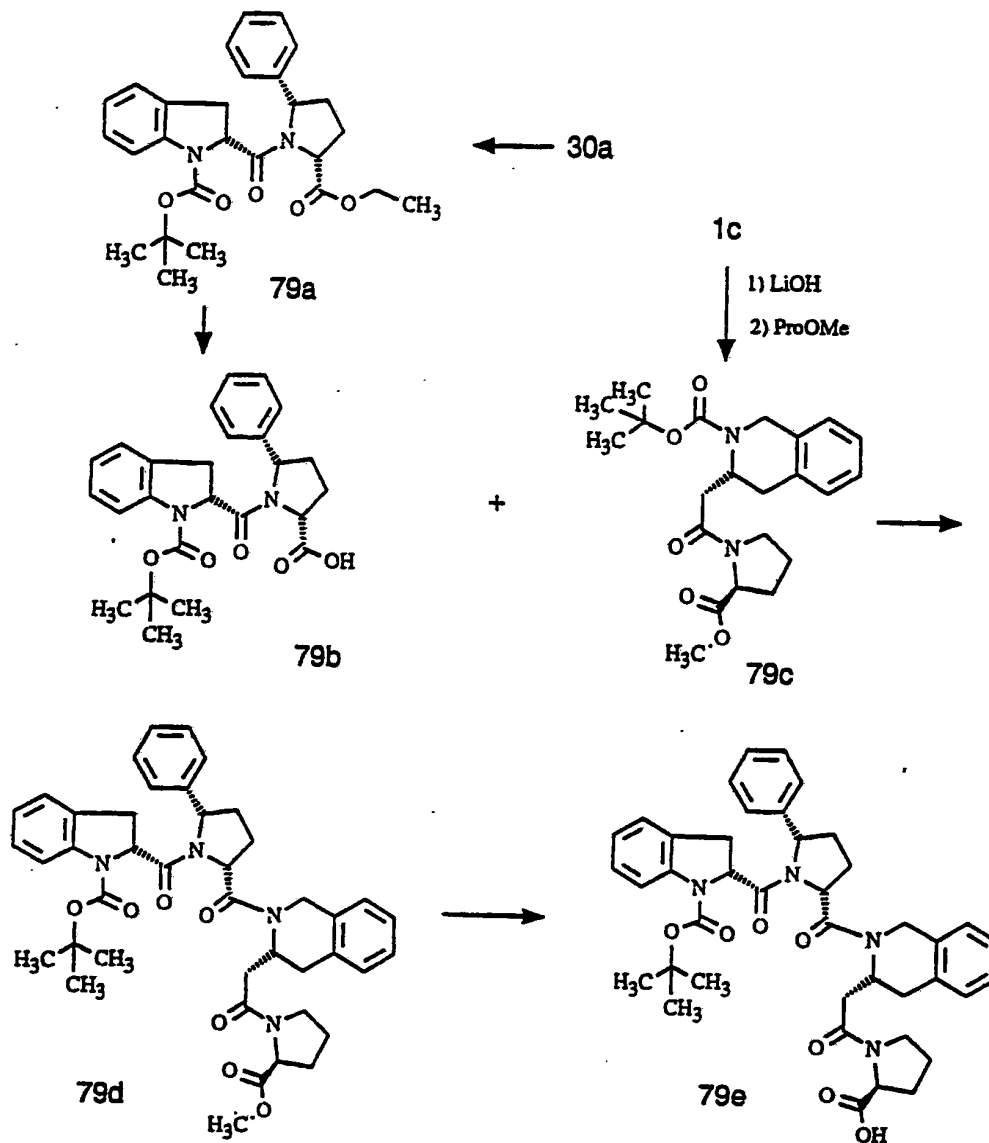
**78c (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 78b on a 0.35 mmol scale following the method described for 1f. The product was isolated in 45% yield (95 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:3 v/v/v).

HPLC System A  $t_R$ =15.7' >99%

Mass spec (FAB)  $m/e$ =610 [M+H]<sup>+</sup>

## EXAMPLE 79



**79a** Ethyl (2R,5S)-1-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylate.

This was prepared from **30a** on a 1.37 mmol scale following the method described for **48b**. The product was isolated in 86% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

$R_f$  (EtOAc:hexane 40:60 v/v) 0.29



**79b** (2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylic acid.

This was prepared from 79a on a 1.18 mmol scale following the method described for 1f. The product was isolated in 66% yield and used without further purification.

R<sub>f</sub> (EtOAc:hexane:AcOH 80:20:2 v/v/v) 0.31

**79c** Methyl N-((3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-acetyl)-proline.

This was prepared from 1b on a 1.25 mmol scale in two steps. 1b was hydrolysed following the method described for 1f, and the crude acid was coupled to ProOMe following the method described for 1d. The product was isolated in 86% yield after flash chromatography on silica gel (eluant EtOAc:hexane 60:40 v/v).

R<sub>f</sub> (EtOAc:hexane 60:40 v/v) 0.23

**79d** Methyl N-((3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetyl)-proline.

This was prepared from 79c on a 0.14 mmol scale in two steps. 79c was deprotected following the method described for 1c, and the crude amine was coupled to 79b following the method described for 1d. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

R<sub>f</sub> (EtOAc:hexane 80:20 v/v) 0.19

**79e** N-((3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetyl)-proline.

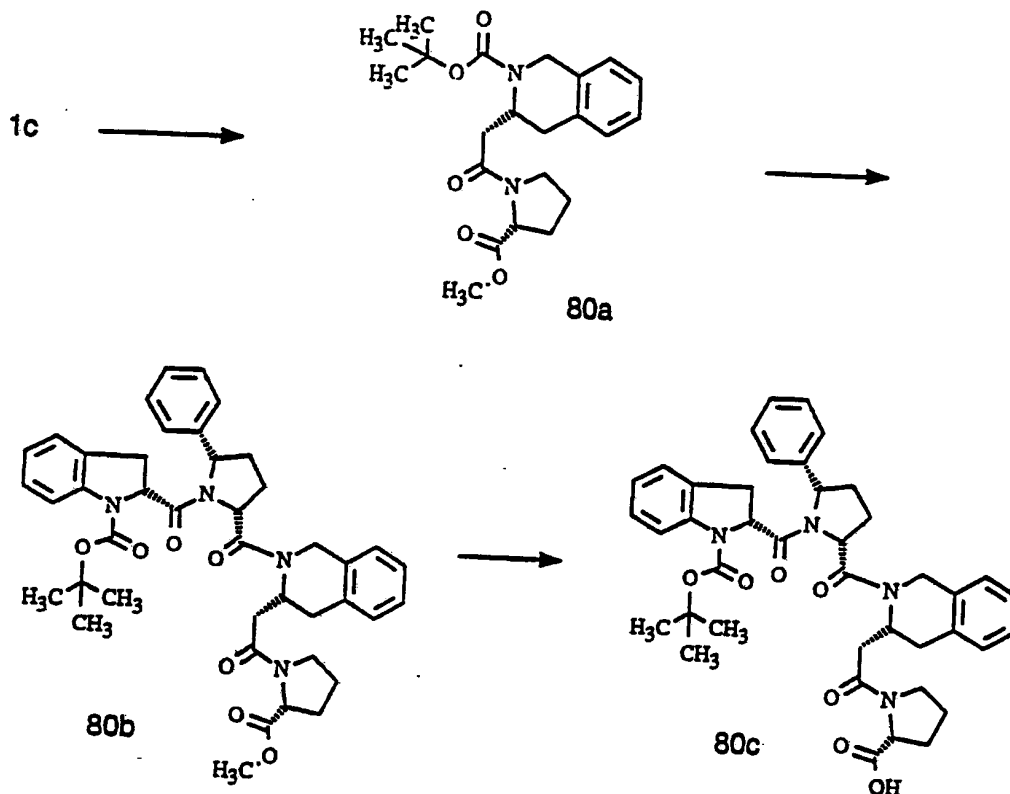
This was prepared from 79d on a 0.14 mmol scale following the method described for 1f. The product was isolated in 45% yield (45 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A t<sub>R</sub>=18.5' >98%

AAA Peptide content=91%

Mass spec (FAB) m/e=707 [M+H]<sup>+</sup>

## EXAMPLE 80



**80a** Methyl N-[(3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-acetyl]-D-prolinate.

This was prepared from 1b on a 1.25 mmol scale following the method described for 79c using D-ProOMe. The product was isolated in 43% yield after flash chromatography on silica gel (eluant EtOAc:hexane 70:30 v/v).

R<sub>f</sub> (EtOAc:hexane 60:40 v/v) 0.27

**80b** Methyl N-((3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetyl)-D-prolinate.

This was prepared from 80a on a 0.13 mmol scale following the method described for 79d. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

R<sub>f</sub> (EtOAc:hexane 80:20 v/v) 0.18

**80c** N-((3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetyl)-D-proline.

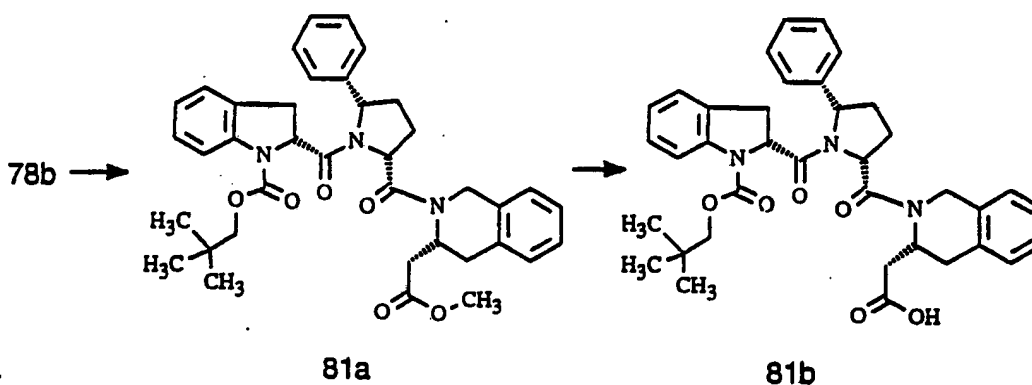
This was prepared from 80b on a 0.13 mmol scale following the method described for 1f. The product was isolated in 50% yield (49 mg) after flash chromatography on silica gel (eluant CHCl<sub>3</sub>:MeOH:AcOH 50:2:1 v/v/v).

HPLC System A t<sub>R</sub>=17.8' >98%

AAA Peptide content=91%

Mass spec (FAB) m/e=707 [M+H]<sup>+</sup>

## EXAMPLE 81



**81a** Methyl (3R)-2-((2R,5S)-1-((2R)-1-neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 78b on a 0.27 mmol scale in two steps. 78b was deprotected following the method described for 1c, and the crude amine was reacted with neopentyl chloroformate following the method described for 72a (excluding the final hydrolysis).

The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

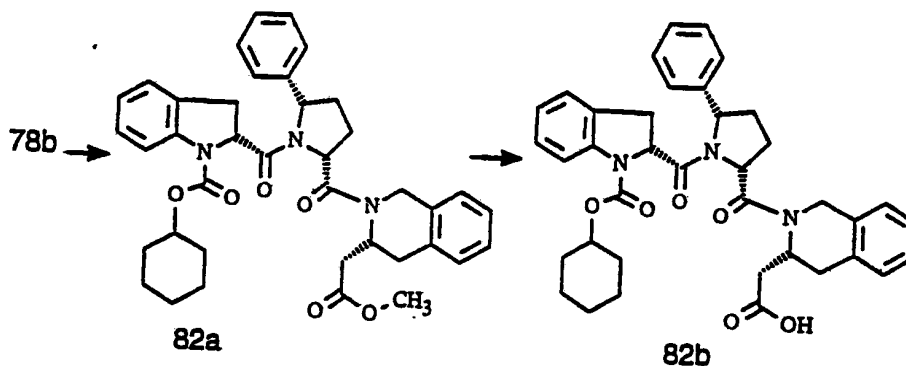
**81b** (3R)-2-((2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 81a on a 0.19 mmol scale following the method described for 1f. The product was isolated in 70% yield (82 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System B  $t_R$ =17.5' >95%

Mass spec (FAB)  $m/e$ =624  $[M+H]^+$

## EXAMPLE 82



**82a** Methyl (3R)-2-((2R,5S)-1-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 78b on a 0.27 mmol scale following the method described for 81a using cyclohexanol instead of neopentyl alcohol. The product was isolated in 62% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

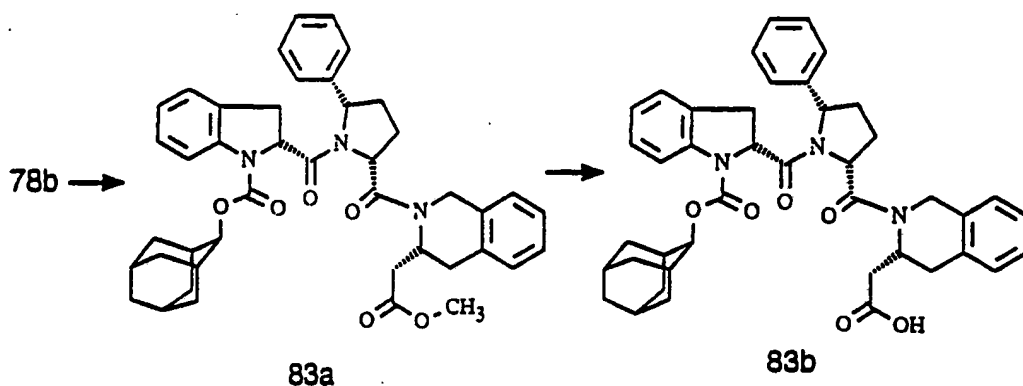
**82b** (3R)-2-((2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 82a on a 0.17 mmol scale following the method described for 1f. The product was isolated in 82% yield (86 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System B  $t_R=18.1'$  >98%

Mass spec (FAB)  $m/e=636$   $[M+H]^+$

### EXAMPLE 83



**83a** Methyl (3R)-2-((2R,5S)-1-((2R)-1-(2-adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 78b on a 0.27 mmol scale following the method described for 81a using 2-adamantanol instead of neopentyl alcohol. The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

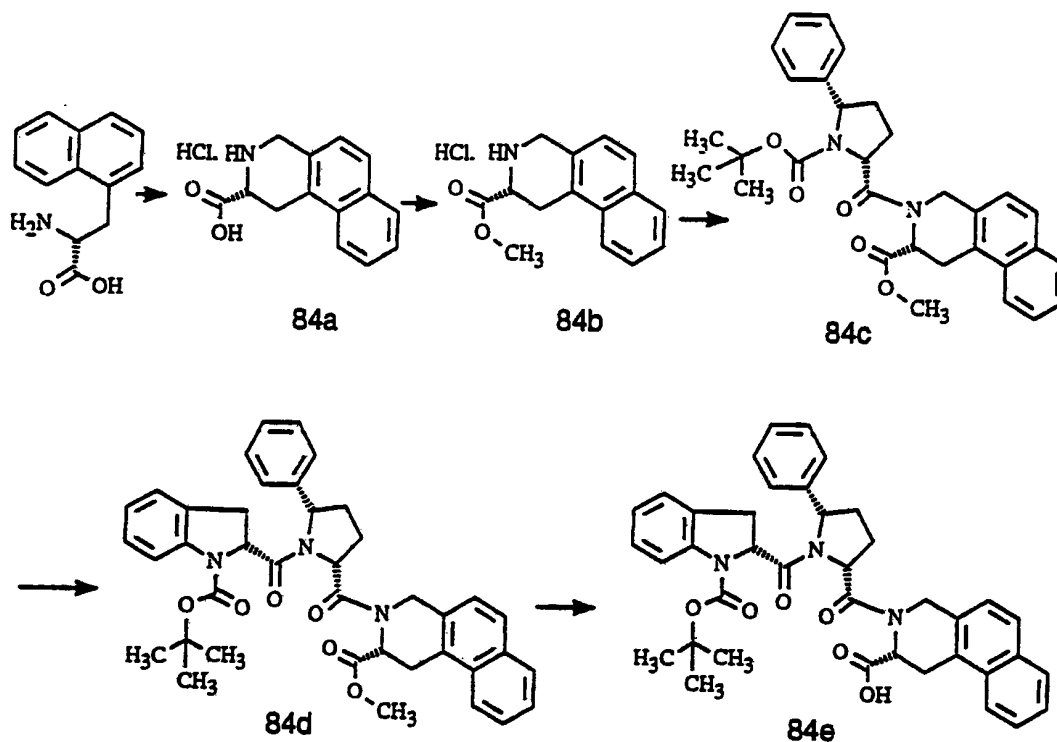
**83b** (3R)-2-((2R,5S)-1-((2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 83a on a 0.19 mmol scale following the method described for 1f. The product was isolated in 66% yield (88 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System B  $t_R=21.4'$  >99%

Mass spec (FAB)  $m/e=687$   $[M]^+$

## EXAMPLE 84

**84a (3R)-1,2,3,4-Tetrahydro-benz[f]isoquinoline-3-carboxylic acid hydrochloride.**

A mixture of D-3-(1-naphthyl)-alanine (5 g, 23.2 mmol), 37% formalin (9 mL) and conc. HCl (40 mL) was heated on a steam bath for 30 min. with occasional swirling. Further formalin (6 mL) and HCl (15 mL) were added and heating was continued for 3 hrs. The mixture was cooled to 4°C and allowed to stand for 2 hrs. The solid product was collected, washed with cold H<sub>2</sub>O and acetone, and dried over KOH to give the title compound (3.2 g, 52%).

**84b Methyl (3R)-1,2,3,4-tetrahydro-benz[f]isoquinoline-3-carboxylate hydrochloride.**

This was prepared from 84a on a 6.05 mmol scale following the method described for 26a. The product was isolated in 43% yield after flash chromatography of the free amine on silica gel (eluant EtOAc) and stored as the hydrochloride.

**84c Methyl (3R)-2-((2R,5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylate.**

This was prepared from 67b and 84b on a 0.50 mmol scale following the method described for 1d. The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**84d Methyl (3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylate.**

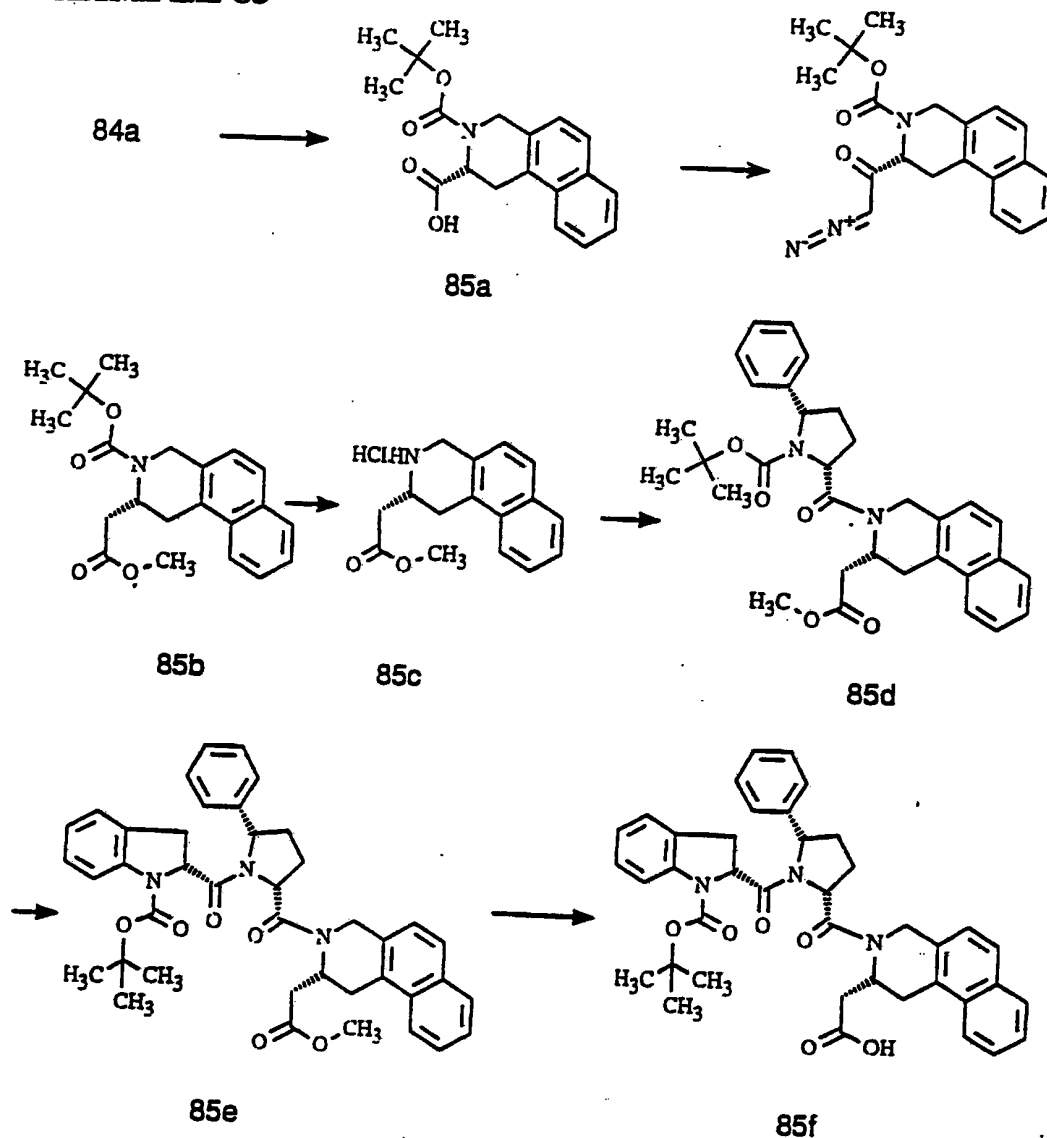
This was prepared from 84c on a 0.41 mmol scale following the method described for 48b. The product was isolated in 81% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

**84e (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid.**

This was prepared from 84d on a 0.33 mmol scale following the method described for 1f. The product was isolated in 74% yield (157 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A  $t_R$ =23.0' >98%

Mass spec (FAB)  $m/e$ =646 [M+H]<sup>+</sup>

**EXAMPLE 85**

**85a** (3R)-2-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid.

This was prepared from 84a on a 6.05 mmol scale following the method described for 1a. The product was isolated in 41% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).



**85b Methyl (3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetate.**

This was prepared from 85a on a 2.5 mmol scale following the method described for 1b. The intermediate diazoketone was isolated in 80% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v), and the product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 18:82 v/v).

**85c Methyl (3R)-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetate hydrochloride.**

This was prepared from 85a on a 0.49 mmol scale following the method described for 1c. The product was used without purification assuming a yield of 100%.

**85d Methyl (3R)-2-((2R,5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetate.**

This was prepared from 67b and 85c on a 0.49 mmol scale following the method described for 1d. The product was isolated in 81% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**85e Methyl (3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetate.**

This was prepared from 85d on a 0.40 mmol scale following the method described for 48b. The product was isolated in 87% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

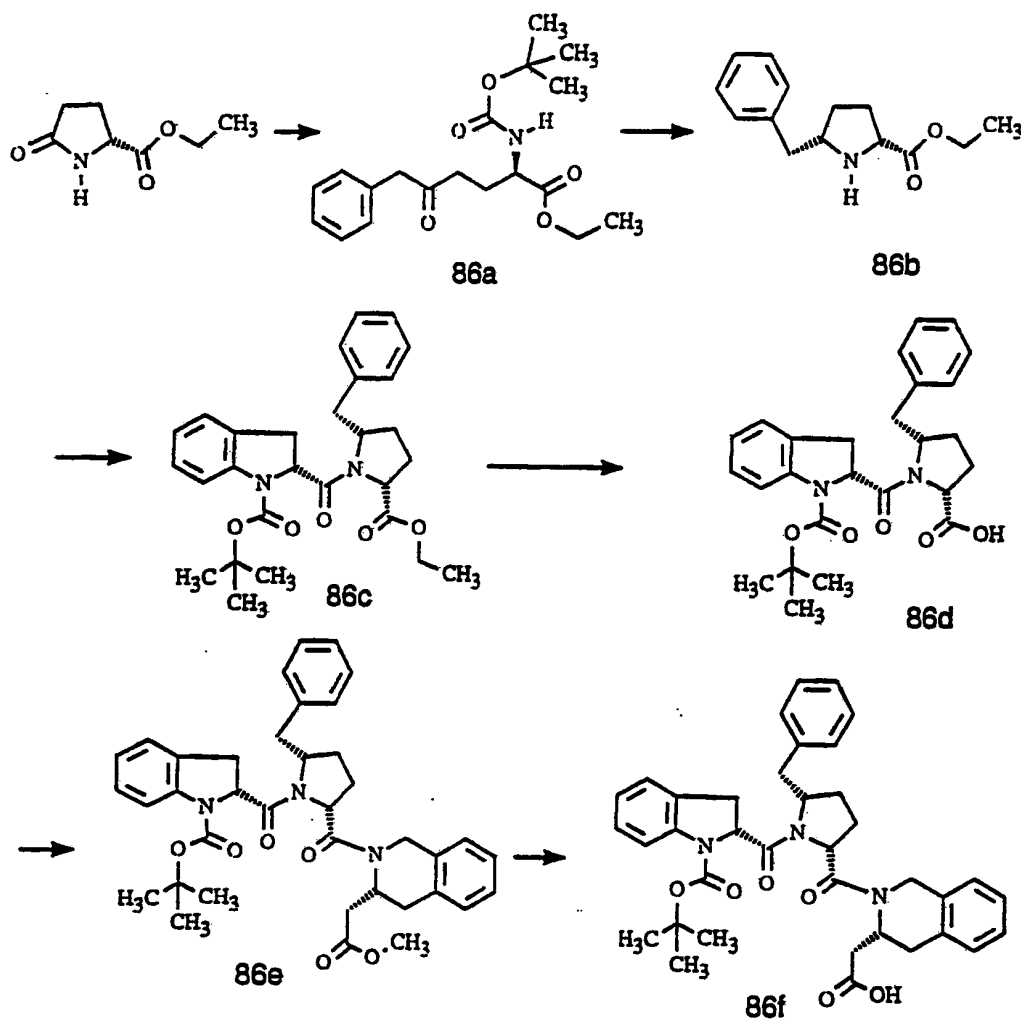
**85f (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetic acid.**

This was prepared from 85e on a 0.36 mmol scale following the method described for 1f. The product was isolated in 64% yield (151 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A  $t_R$ =24.1' >99%

Mass spec (FAB)  $m/e$ =560 [M+H-BOC]<sup>+</sup>

## EXAMPLE 86

**86a Ethyl (2R)-2-tert-butyloxycarbonylamino-5-oxo-6-phenyl-hexanoate.**

To a stirred solution of ethyl N-BOC-D-pyrroglutamate (2.06 g, 8 mmol) in THF (10 mL), cooled to  $-78^{\circ}\text{C}$  under  $\text{N}_2$ , was added dropwise a solution of benzylmagnesium chloride in THF (5 mL, 2N, 10 mmol). The mixture was allowed to warm to room temperature over 1 hr., and was then poured into 5% aq.  $\text{KHSO}_4$ . The mixture was extracted with EtOAc, and the organic phase was washed with satd.  $\text{KHCO}_3$  and brine, filtered (Whatman<sup>®</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v) to give the title compound (1.5 g, 54%).

$^1\text{H}$  NMR  $\delta$  1.28 (3H,t,J=7Hz); 1.47 (9H,s); 3.73 (2H,s); 4.19 (2H,q,J=7Hz)

**86b Ethyl (2R,5S)-5-benzyl-pyrrolidine-2-carboxylate.**

A solution of 86a (1.5 g, 4.3 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) and TFA (20 mL) was stirred at  $0^\circ\text{C}$  for 1 hr. then concentrated *in vacuo*. finally with  $\text{CCl}_4$  azeotrope. The residue was taken up in EtOH (30 mL). To this solution was added AcOH (3 mL), then diisopropylethylamine (0.87 mL, 5 mmol) and finally  $\text{NaBH}_3\text{CN}$  (0.82 g, 13 mmol) in three portions. The mixture was stirred at room temperature for 3 hr., then the solvent was evaporated *in vacuo*. The residue was partitioned between EtOAc and satd.  $\text{KHCO}_3$ , and the organic phase was washed with brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 60:40 v/v) to give the title compound (410 mg, 41%).

$^1\text{H}$  NMR  $\delta$  1.28 (3H,t,J=7Hz); 2.75 (1H,dd,J=14,7Hz); 2.89 (1H,dd,J=14,7Hz); 4.19 (2H,q,J=7Hz)

**86c Ethyl (2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carboxylate.**

This was prepared from 86b on a 1.76 mmol scale following the method described for 48b. The product was isolated in 86% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**86d (2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carboxylic acid.**

This was prepared from 86c on a 1.51 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**86e Methyl (3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 1c and 86d on a 0.50 mmol scale following the method described for 1d. The product was isolated in 97% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

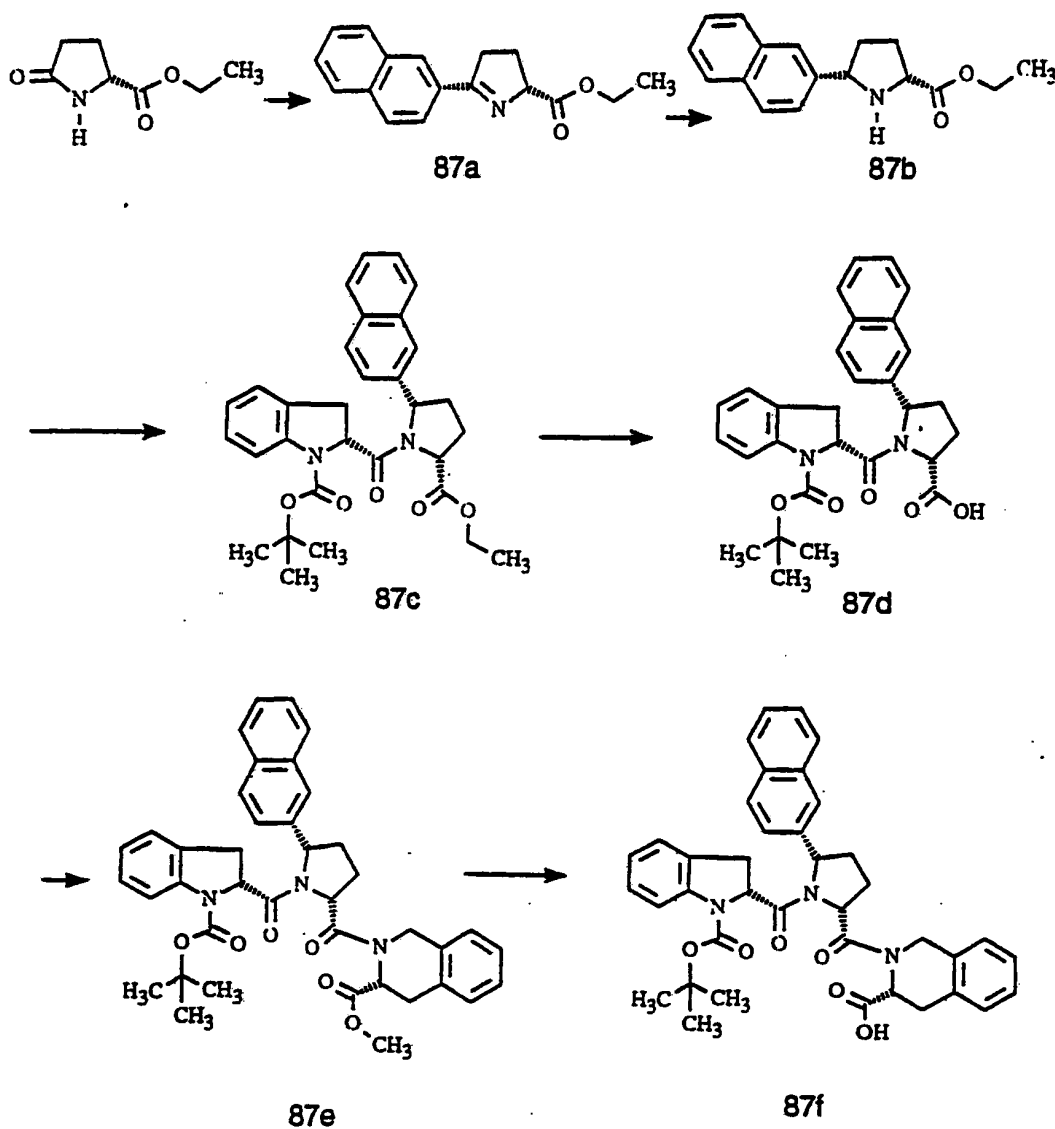
**86f (3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-benzyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 86e on a 0.49 mmol scale following the method described for 1f. The product was isolated in 49% yield (150 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A  $t_R$ =15.2' >99%

Mass spec (FAB)  $m/e$ =624  $[M+H]^+$

### EXAMPLE 87



**87a Ethyl (2R)-3,4-dihydro-5-(2-naphthyl)-2H-pyrrole-2-carboxylate.**

To a stirred solution of ethyl N-BOC-D-pyrroglutamate (2.06 g, 8 mmol) in THF (10 mL), cooled to  $-78^{\circ}\text{C}$  under  $\text{N}_2$ , was added dropwise a solution of 2-naphthylmagnesium chloride in THF (5 mL, 2N, 10 mmol). The mixture was allowed to warm to room temperature over 1 hr., and was then poured into 5% aq.  $\text{KHSO}_4$ . The mixture was extracted with EtOAc, and the organic phase was washed with satd.  $\text{KHCO}_3$  and brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was taken up in  $\text{CH}_2\text{Cl}_2$  (20 mL) and TFA (20 mL) and stirred at  $0^{\circ}\text{C}$  for 1 hr. then concentrated *in vacuo*, finally with  $\text{CCl}_4$  azeotrope. The residue was taken up in satd.  $\text{KHCO}_3$  and extracted twice with EtOAc. The combined organic phases were washed with brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 then 40:60 v/v) to give the title compound (605 mg, 28%).

$^1\text{H}$  NMR  $\delta$  1.43 (3H,t,J=7Hz); 4.41 (2H,q,J=7Hz); 5.04 (1H,m)

**87b Ethyl (2R,5S)-5-(2-naphthyl)-pyrrolidine-2-carboxylate.**

This was prepared from 87a on a 2.27 mmol scale following the method described for 30a. The product was isolated in 56% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

$^1\text{H}$  NMR  $\delta$  1.43 (3H,t,J=7Hz); 4.08 (1H,m); 4.35 (2H,q,J=7Hz); 4.48 (1H,m)

**87c Ethyl (2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carboxylate.**

This was prepared from 87b on a 1.26 mmol scale following the method described for 48b. The product was isolated in 99% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**87d (2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carboxylic acid.**

This was prepared from 87c on a 1.25 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**87e Methyl (3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

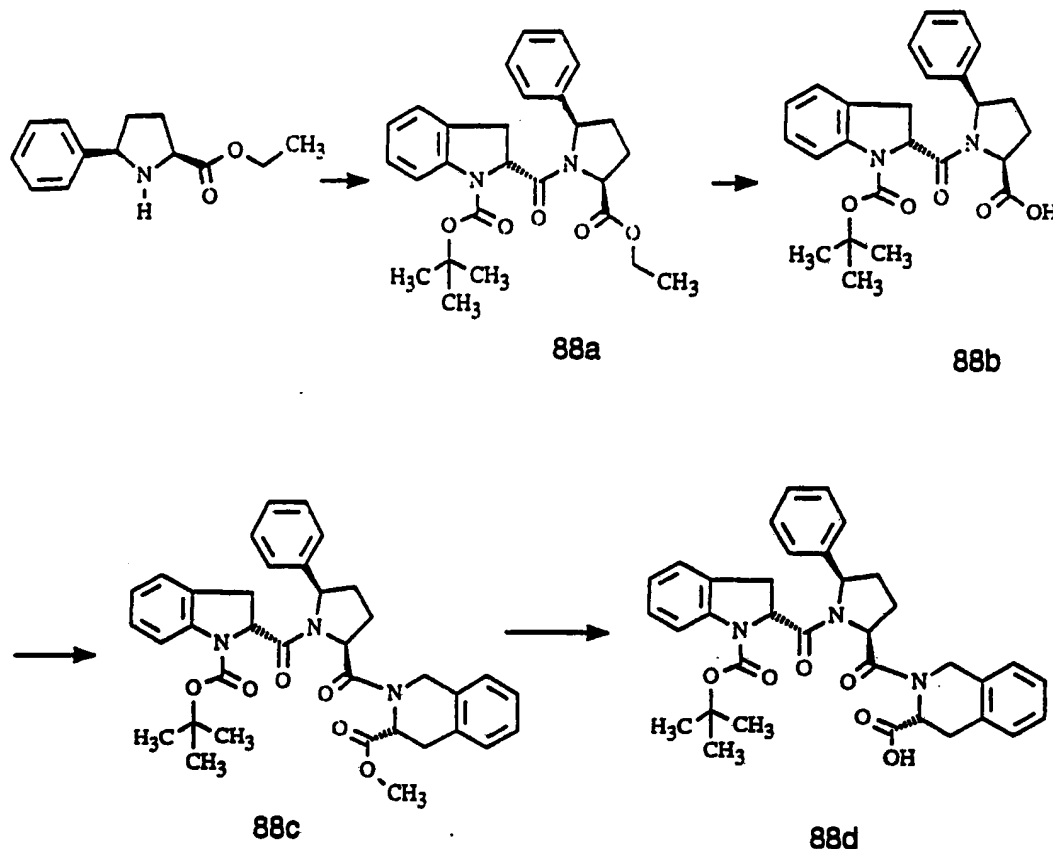
This was prepared from 26a and 86d on a 0.31 mmol scale following the method described for 1d. The product was isolated in 95% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

**87f (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 87e on a 0.30 mmol scale following the method described for 1f. The product was isolated in 48% yield (93 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A  $t_R$ =16.5' >98%

Mass spec (FAB)  $m/e$ =646  $[M+H]^+$

**EXAMPLE 88**

**88a** Ethyl (2S,5R)-1-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylate.

This was prepared from ethyl (2S,5R)-5-phenyl-pyrrolidine-2-carboxylate (the enantiomer of 30a) following the method described for 48b. The product was isolated in 97% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

$R_f$  (EtOAc:hexane 40:60 v/v) 0.27

**88b** (2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylic acid.

This was prepared from 88a following the method described for 1f. The product was isolated in 69% yield and was used without further purification.

$R_f$  (EtOAc:hexane:AcOH 80:20:2 v/v/v) 0.38

**88c** Methyl (3R)-2-((2S,5R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 26a and 88b on a 0.20 mmol scale following the method described for 1d. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

R<sub>f</sub> (EtOAc:hexane 50:50v/v) 0.24

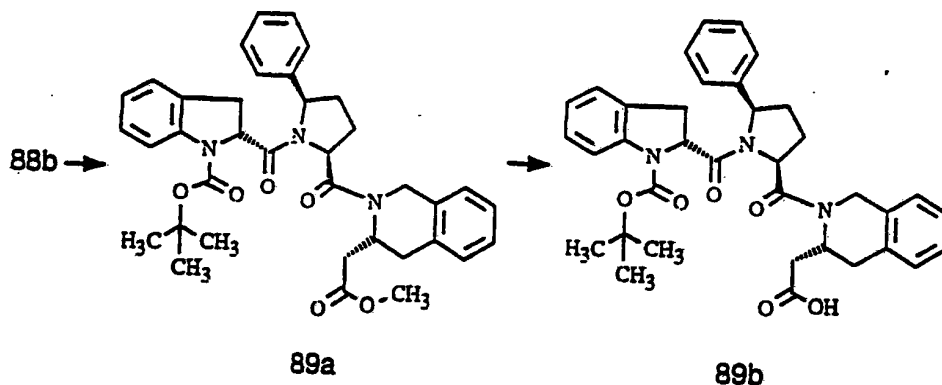
**88d** (3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 88c on a 0.20 mmol scale following the method described for 1f. The product was isolated in 55% yield (66 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

HPLC System A t<sub>R</sub>=19.8' >98%

Mass spec (FAB) m/e=595 [M]<sup>+</sup>

## EXAMPLE 89



**89a** Methyl (3R)-2-((2S,5R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c and 88b on a 0.20 mmol scale following the method described for 1d. The product was isolated in 87% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

R<sub>f</sub> (EtOAc:hexane 50:50v/v) 0.26



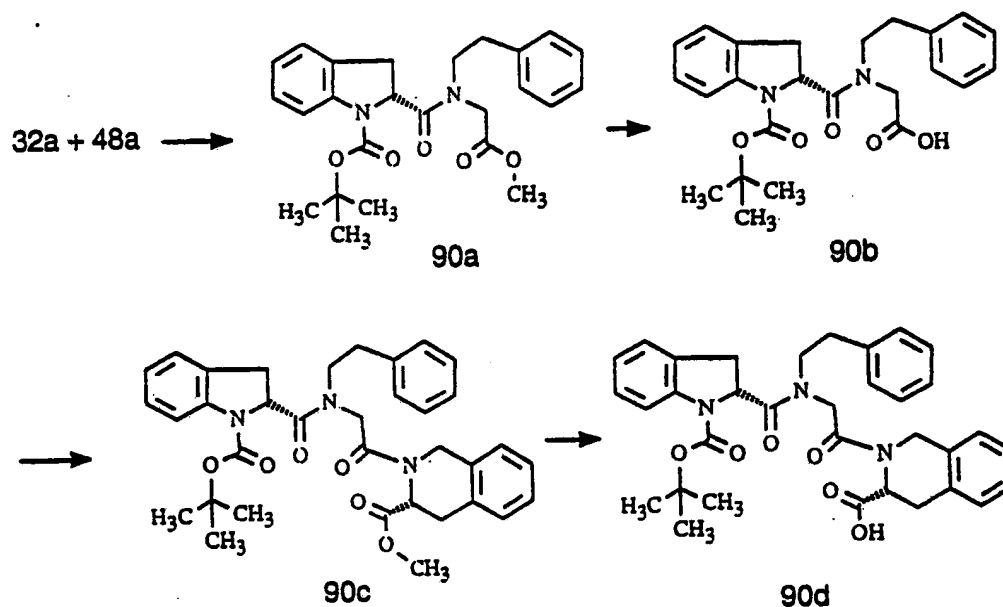
**89b (3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 89a on a 0.17 mmol scale following the method described for 1f. The product was isolated in 53% yield (55 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

HPLC System A  $t_R$ =20.3' >95%

Mass spec (FAB)  $m/e$ =610  $[M+H]^+$

## EXAMPLE 90



**90a Methyl N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 32a and 48a on a 0.70 mmol scale following the method described for 1d. The product was isolated in 88% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**90b N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 90a on a 0.50 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**90c Methyl (3R)-2-[N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 90b and 26a on a 0.50 mmol scale following the method described for 1d. The product was isolated in 54% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

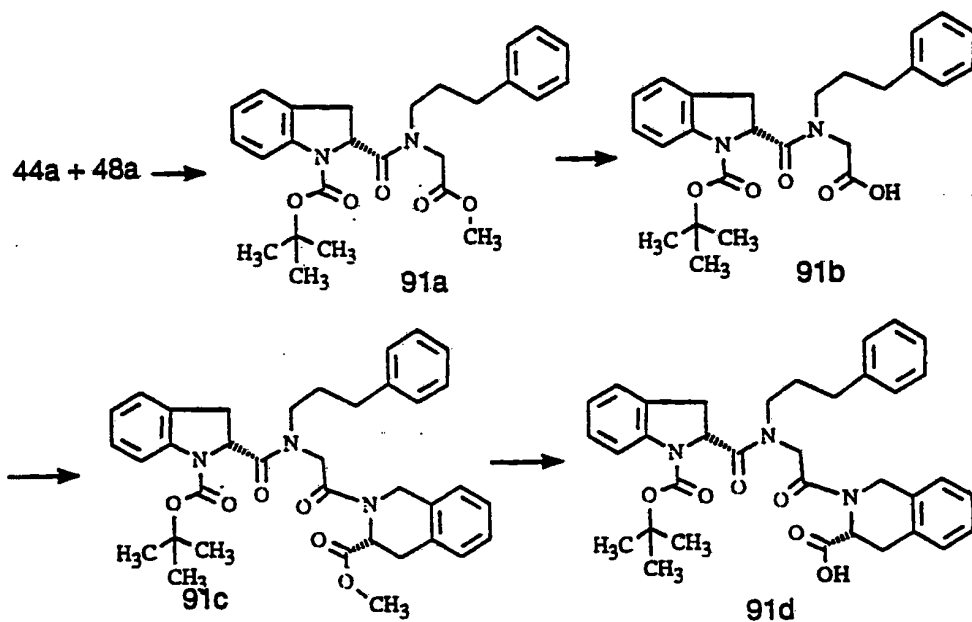
**90d (3R)-2-[N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 90c on a 0.27 mmol scale following the method described for 1f. The product was isolated in 72% yield (114 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A  $t_R$ =19.9' >99%

Mass spec (FAB)  $m/e$ =584  $[M+H]^+$

## EXAMPLE 91



**91a Methyl N-3-phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 44a and 48a on a 3.52 mmol scale following the method described for 1d. The product was isolated in 55% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R<sub>f</sub> (EtOAc:hexane 40:60 v/v) 0.31

**91b**      **N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 91a on a 0.98 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**91c**      **Methyl (3R)-2-{N-3-phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 26a and 91b on a 0.98 mmol scale following the method described for 1d. The product was isolated in 25% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

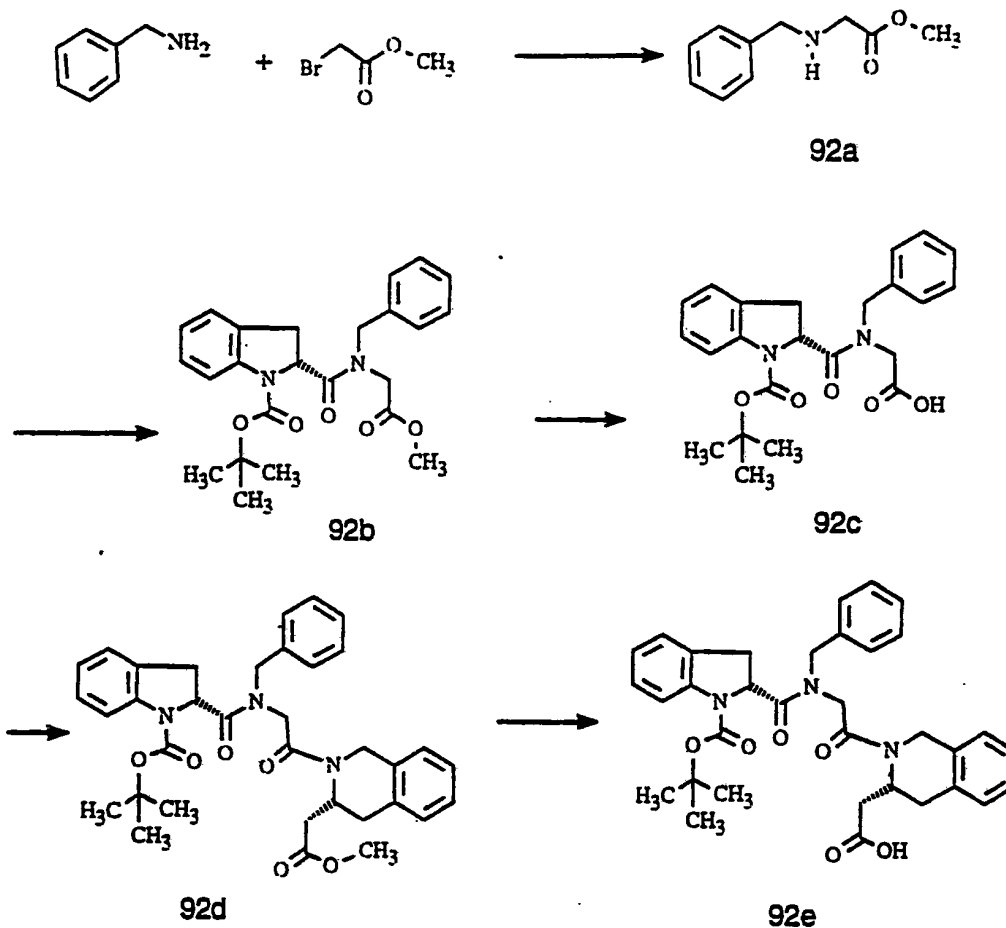
R<sub>f</sub> (EtOAc:hexane 40:60 v/v) 0.17

**91d (3R)-2-{N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 91c on a 0.25 mmol scale following the method described for 1f. The product was isolated in 43% yield (65 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:1 v/v/v).

HPLC System A t<sub>R</sub>=20.1' >98%

Mass spec (FAB) m/e=598 [M+H]<sup>+</sup>

**EXAMPLE 92****92a Methyl N-benzyl-glycinate.**

This was prepared from benzylamine on a 4.58 mmol scale following the method described for 32a. The product was isolated in 95% yield and used without further purification.

**92b Methyl N-benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 92a and 48a on a 4.37 mmol scale following the method described for 1d. The product was isolated in 65% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

$R_f$  (EtOAc:hexane 40:60 v/v) 0.38

**92c** N-Benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from 92b on a 1.43 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**92d** Methyl (3R)-2-{N-benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c and 92c on a 1.43 mmol scale following the method described for 1d. The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R<sub>f</sub> (EtOAc:hexane 40:60 v/v) 0.18

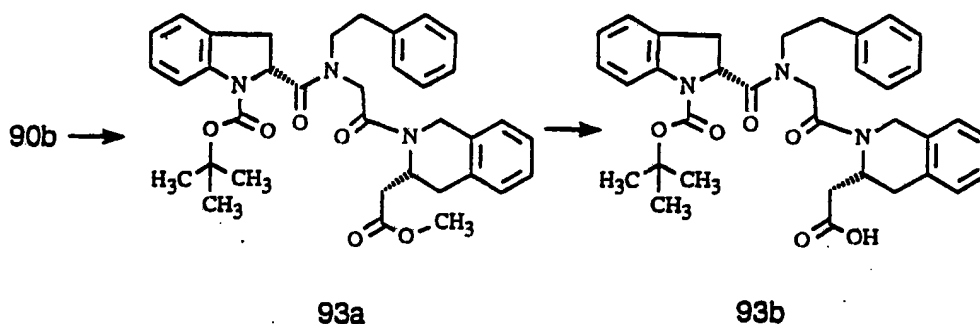
**92e** (3R)-2-{N-Benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 92d on a 1.07 mmol scale following the method described for 1f. The product was isolated in 59% yield (374 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:1 v/v/v).

HPLC System A t<sub>R</sub>=19.4' >95%

Mass spec (FAB) m/e=584 [M+H]<sup>+</sup>

### EXAMPLE 93



**93a** Methyl (3R)-2-{N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c and 90b on a 0.41 mmol scale following the method described for 1d. The product was isolated in 83% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

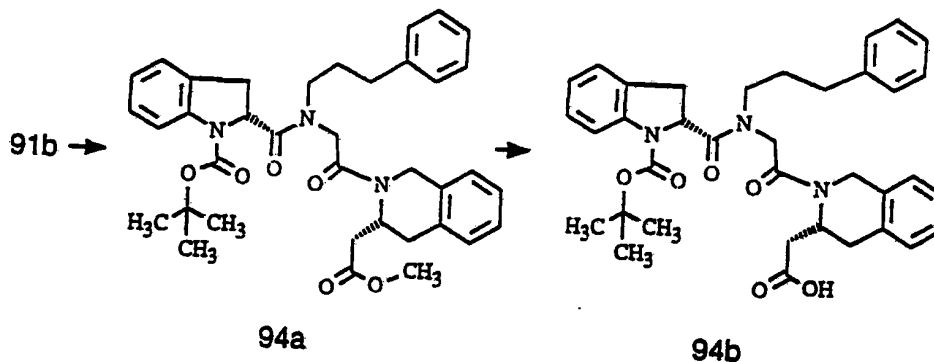
93b (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 93a on a 0.34 mmol scale following the method described for 1f. The product was isolated in 54% yield (110 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 40:60:2 v/v/v).

HPLC System B  $t_R=15.0'$  >95%

Mass spec (FAB)  $m/e=598$   $[M+H]^+$

### EXAMPLE 94



94a Methyl (3R)-2-{N-3-Phenylpropyl-N-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c and 91b on a 0.98 mmol scale following the method described for 1d. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:hexane 45:55 v/v).

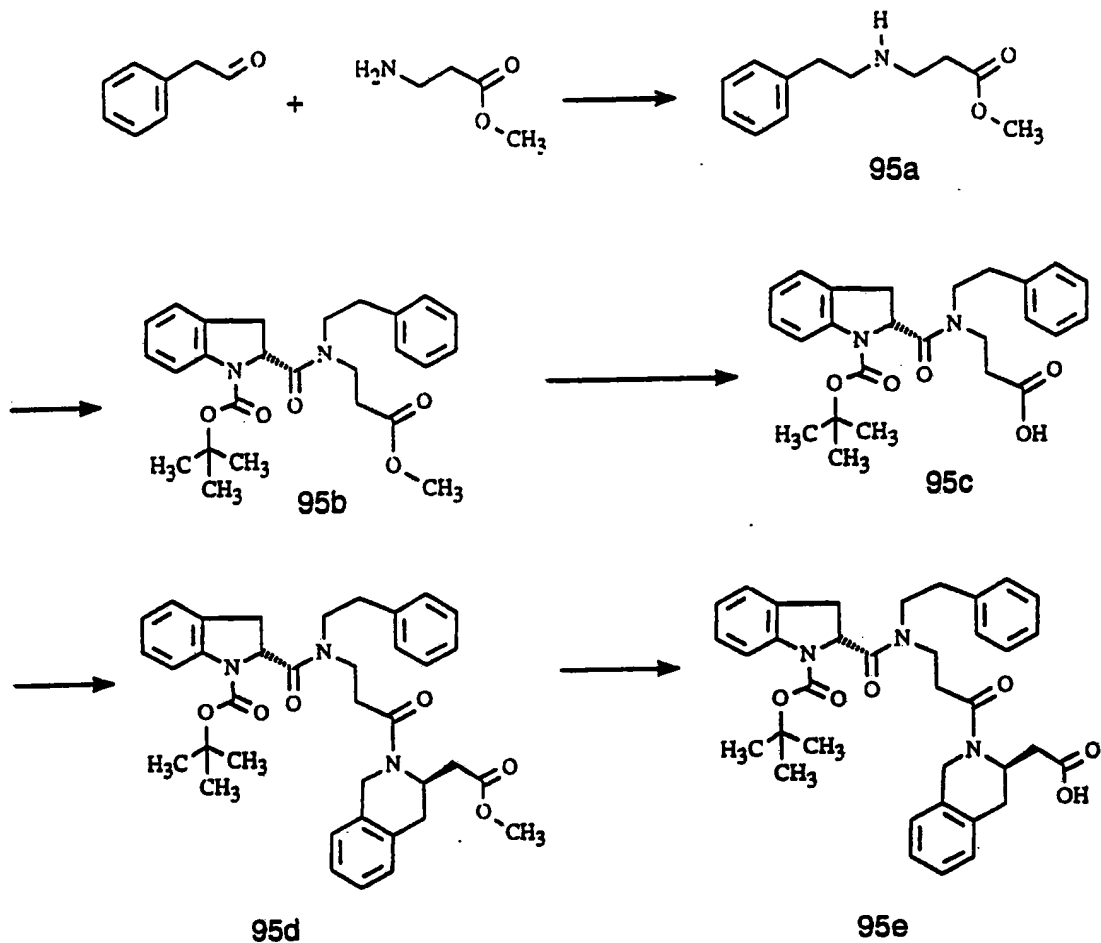
$R_f$  (EtOAc:hexane 45:55 v/v) 0.15

94b (3R)-2-{N-3-Phenylpropyl-N-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 94a on a 0.67 mmol scale following the method described for 1f. The product was isolated in 55% yield (228 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:1 v/v/v).

HPLC System A  $t_R=21.0'$  >98%

Mass spec (FAB)  $m/e=611$   $[M]^+$

**EXAMPLE 95****95a Methyl 3-phenethylamino-propanoate.**

This was prepared from phenylacetaldehyde and β-alanineOMe on a 2.25 mmol scale following the method described for 42a. The product was isolated in 40% yield after flash chromatography on silica gel (eluant CHCl<sub>3</sub>:MeOH:AcOH 35:2:1 v/v/v).

**95b Methyl 3-{N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino}-propanoate.**

This was prepared from 40a and 95a on a 0.92 mmol scale following the method described for 1d. The product was isolated in 63% yield after flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

**95c** 3-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino}-propanoic acid.

This was prepared from 95b on a 0.59 mmol scale following the method described for 1f. The product was isolated in 54% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:1 v/v/v).

HPLC System A  $t_R$ =15.9' >98%

Mass spec (FAB)  $m/e$ =439 [M+H]<sup>+</sup>

**95d** Methyl (3R)-2-{3-[N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino]-propanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 26a and 95c on a 0.15 mmol scale following the method described for 1d. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 60:40 v/v).

$R_f$  (EtOAc:hexane 70:30 v/v) 0.38

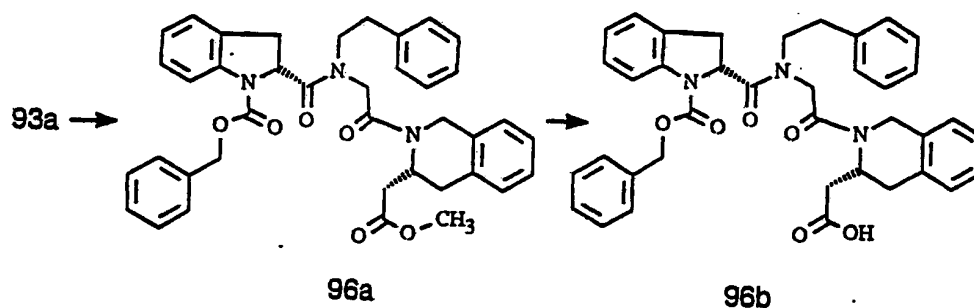
**95e** (3R)-2-{3-[N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino]-propanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 95d on a 0.15 mmol scale following the method described for 1f. The product was isolated in 56% yield (50 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A  $t_R$ =19.3' >95%

Mass spec (FAB)  $m/e$ =598 [M+H]<sup>+</sup>

## EXAMPLE 96





**96a** Methyl(3R)-2-{N-phenethyl-N-((2R)-1-benzyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 93a and benzyl chloroformate on a 0.46 mmol scale following the method described for 81a. The product was isolated in 100% yield and used without further purification.

R<sub>f</sub> (EtOAc:pet. ether 40:60 v/v) 0.17

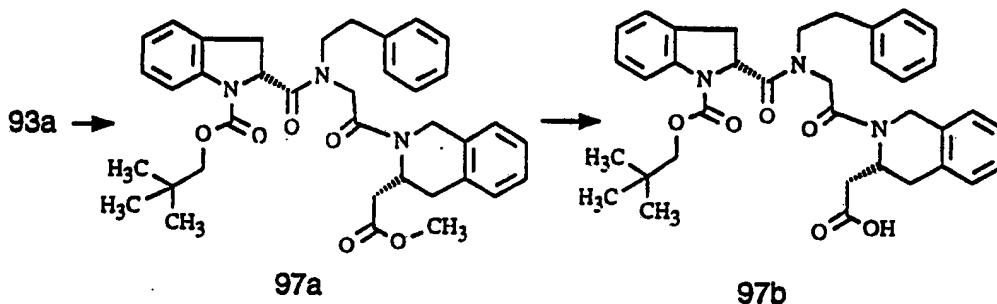
**96b** (3R)-2-{N-Phenethyl-N-((2R)-1-benzyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 96a on a 0.46 mmol scale following the method described for 1f. The product was isolated in 67% yield (194 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:1 v/v/v).

HPLC System B t<sub>R</sub>=14.8' >98%

Mass spec (FAB) m/e=441 [M+H-Cmt]<sup>+</sup>

## EXAMPLE 97



**97a** Methyl (3R)-2-{N-phenethyl-N-((2R)-1-neopentylloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 93a on a 0.46 mmol scale following the method described for 81a. The product was isolated in 100% yield and used without further purification.

R<sub>f</sub> (EtOAc:pet. ether 40:60 v/v) 0.21

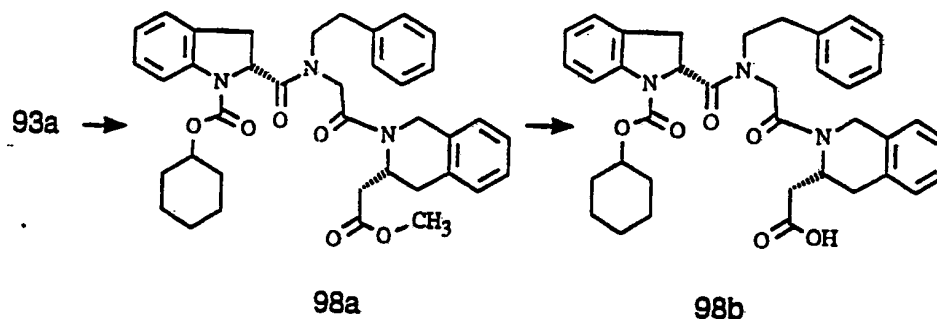
**97b** (3R)-2-{N-Phenethyl-N-((2R)-1-neopentylloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 97a on a 0.46 mmol scale following the method described for 1f. The product was isolated in 35% yield (101 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:1 v/v/v).

HPLC System B  $t_R$ =16.2' >90%

Mass spec (FAB)  $m/e$ =612  $[M+H]^+$

### EXAMPLE 98



**98a**      Methyl      (3R)-2-{N-phenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

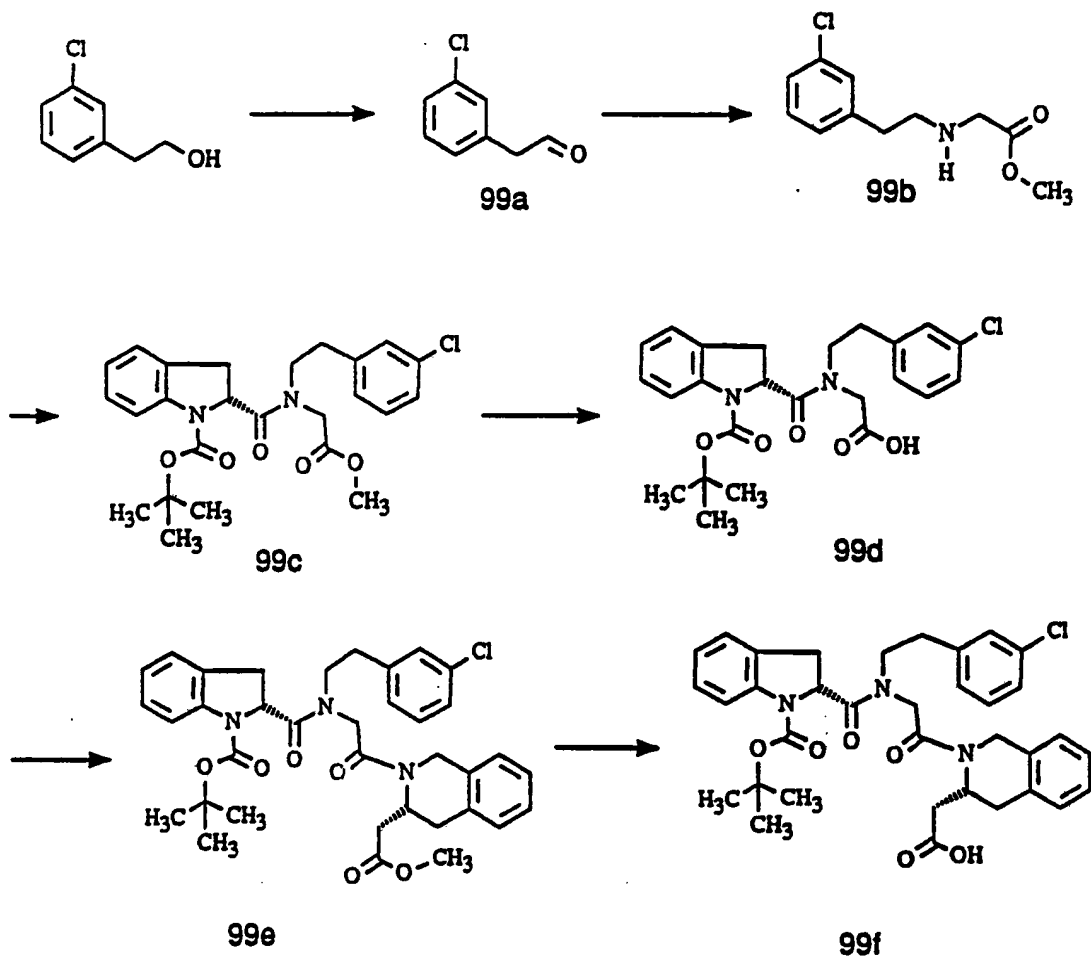
This was prepared from 93a on a 0.46 mmol scale following the method described for 82a. The product was isolated in 100% yield and used without further purification.

**98b**      (3R)-2-{N-Phenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 98a on a 0.46 mmol scale following the method described for 1f. The product was isolated in 25% yield (74 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:1 v/v/v).

HPLC System B  $t_R$ =17.6' >90%

Mass spec (FAB)  $m/e$ =624  $[M+H]^+$

**EXAMPLE 99****99a 3-Chlorophenylacetaldehyde.**

This was prepared from 3-chlorophenethyl alcohol on a 9.58 mmol scale using the standard Swern oxidation conditions (A.J. Mancuso *et al*, *J.Org.Chem.*, 43, 2480, 1978). The product was used without purification assuming a yield of 100%.

**99b Methyl N-3-chlorophenethyl-glycinate.**

This was prepared from 99a on a 9.58 mmol scale following the method described for 42a. The product was isolated in 5.5% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

**99c Methyl N-3-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 99b and 48a on a 0.50 mmol scale following the method described for 1d. The product was isolated in 47% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R<sub>f</sub> (EtOAc:hexane 40:60 v/v) 0.29

**99d N-3-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 99c on a 0.24 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**99e Methyl (3R)-2-{N-3-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 1c and 99d on a 0.12 mmol scale following the method described for 1d. The product was isolated in 23% yield after flash chromatography on silica gel (eluant EtOAc:hexane 45:55 v/v).

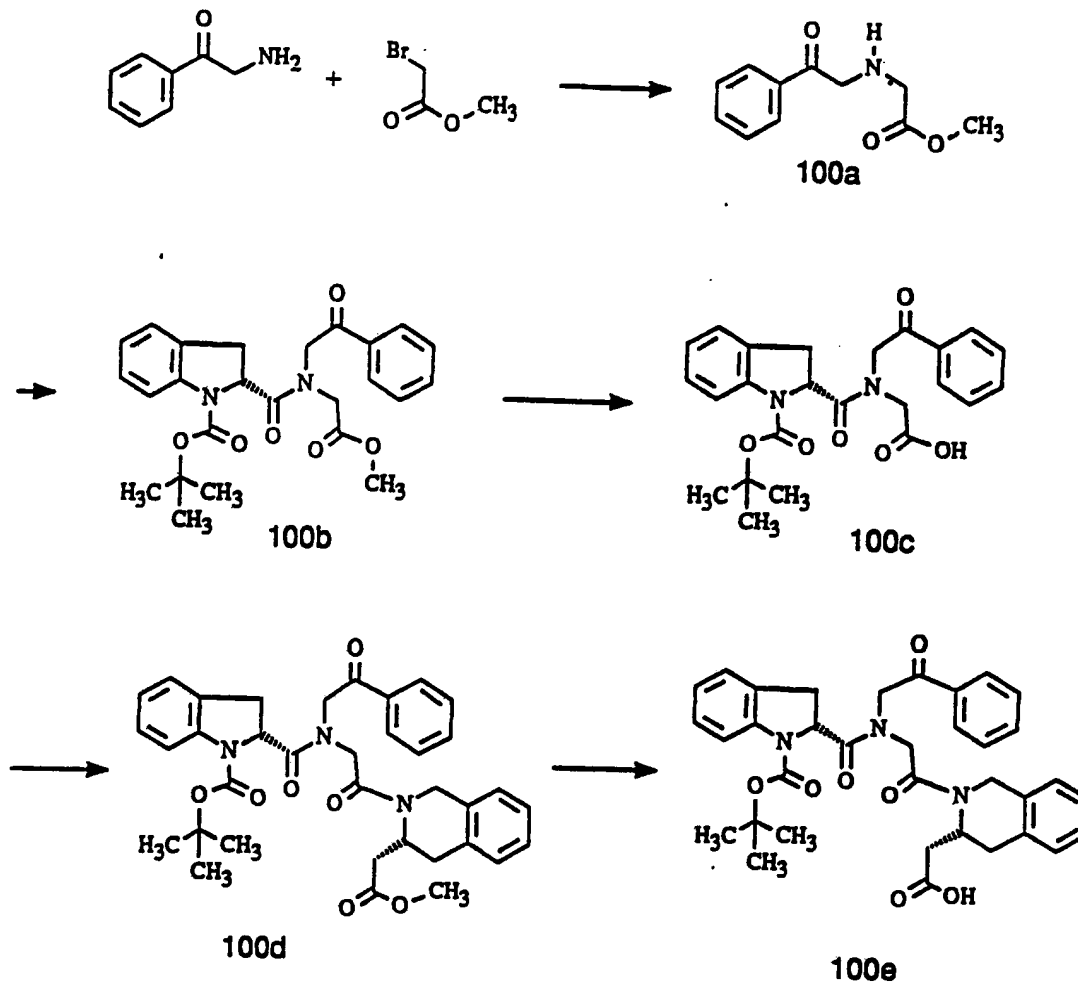
R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.25

**99f (3R)-2-{N-3-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 99e on a 0.028 mmol scale following the method described for 1f. The product was isolated in 71% yield (12 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:2 v/v/v).

HPLC System A t<sub>R</sub>=22.0' >80%

Mass spec (FAB) m/e=632 [M+H]<sup>+</sup>

**EXAMPLE 100****100a Methyl N-(2-oxo-2-phenylethyl)-glycinate.**

This was prepared from 2'-aminoacetophenone hydrochloride on a 11.6 mmol scale following the method described for 32a. The product was isolated in 83% yield after flash chromatography on silica gel (eluant EtOAc:pet.ether 90:10).

$^1\text{H}$  NMR  $\delta$  3.56 (2H,s); 3.70 (3H,s); 4.20 (2H,s); 7.4-7.6 (3H,m); 7.9-8.0 (2H,m)

**100b Methyl N-(2-oxo-2-phenylethyl)-N-((2R)-1-tert-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 100a and 48a on a 0.97 mmol scale following the method described for 1d. The product was isolated in 62% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

$R_f$  (EtOAc:pet. ether 35:65 v/v) 0.31

$^1\text{H}$  NMR  $\delta$  1.56 (9H,2s); 3.74 (3H,2s)

**100c** N-(2-Oxo-2-phenylethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from 100b on a 0.61 mmol scale following the method described for 1f. The product was isolated in 84% yield and used without further purification.

**100d** Methyl (3R)-2-{N-(2-oxo-2-phenylethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c and 100c on a 0.52 mmol scale following the method described for 1d. The product was isolated in 49% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:1 v/v/v).

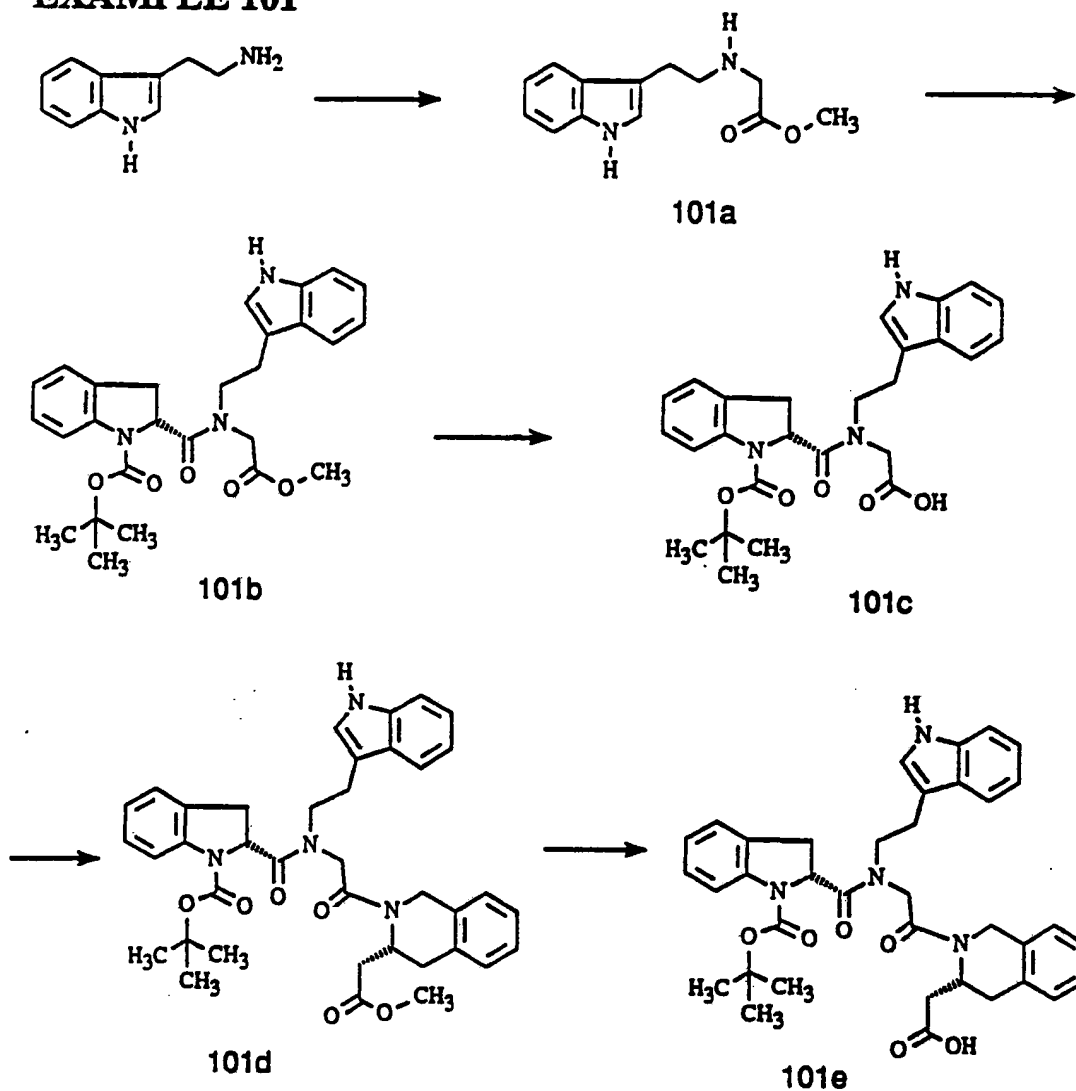
$^1\text{H NMR}$   $\delta$  1.56 (9H,3s); 3.55 (3H,2s)

**100e** (3R)-2-{N-(2-Oxo-2-phenylethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 100d on a 0.26 mmol scale following the method described for 1f. The product was isolated in 71% yield (113 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:1 v/v/v).

HPLC System B  $t_R$ =13.4' >98%

Mass spec (FAB)  $m/e$ =612  $[M+H]^+$

**EXAMPLE 101****101a Methyl N-(2-(3-Indolyl)ethyl)-glycinate.**

This was prepared from tryptamine hydrochloride on a 5.0 mmol scale following the method described for 32a. The product was used without purification, assuming a yield of 100%.

**101b Methyl N-(2-(3-Indolyl)ethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 101a and 48a on a 1.0 mmol scale following the method described for 1d. The product was isolated in 44% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

**101c** N-(2-(3-Indolyl)ethyl)-N-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from 101b on a 0.44 mmol scale following the method described for 1f. The product was isolated in 40% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System A  $t_R$ =10.5' >99%

Mass spec (FAB)  $m/e$ =464 [M+H]<sup>+</sup>

**101d** Methyl (3R)-2-{N-(2-(3-indolyl)ethyl)-N-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c and 101d on a 0.08 mmol scale following the method described for 1d. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v).

$R_f$  (EtOAc:hexane 55:45 v/v) 0.30

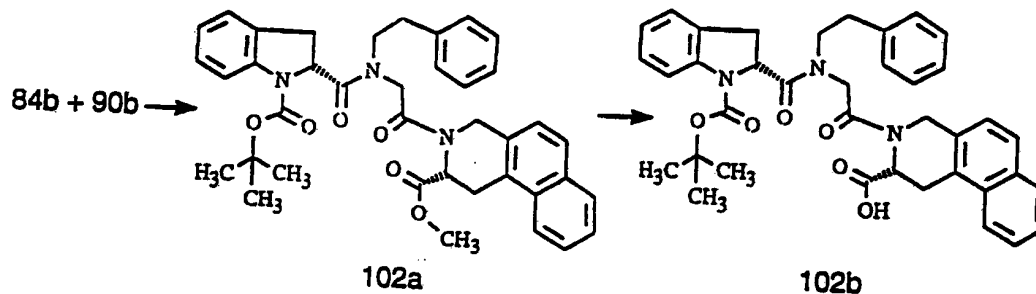
**101e** (3R)-2-{N-(2-(3-Indolyl)ethyl)-N-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 101d on a 0.08 mmol scale following the method described for 1f. The product was isolated in 56% yield (28 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:2 v/v/v).

HPLC System A  $t_R$ =18.2' >95%

Mass spec (FAB)  $m/e$ =659 [M+Na]<sup>+</sup>

## EXAMPLE 102





**102a** Methyl (3R)-2-{N-phenethyl-N-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylate.

This was prepared from 90b and 84b on a 0.46 mmol scale following the method described for 1d. The product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

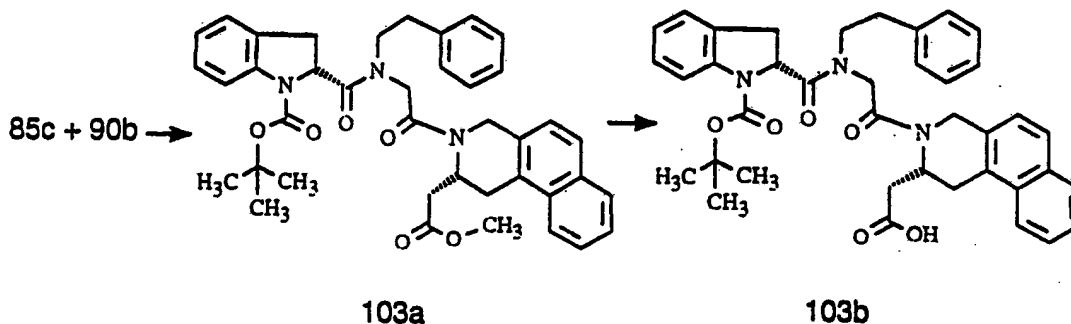
**102b** (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid.

This was prepared from 102a on a 0.32 mmol scale following the method described for 1f. The product was isolated in 68% yield (138 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A  $t_R$ =22.1' >98%

Mass spec (FAB)  $m/e$ =634 [M+H]<sup>+</sup>

### EXAMPLE 103

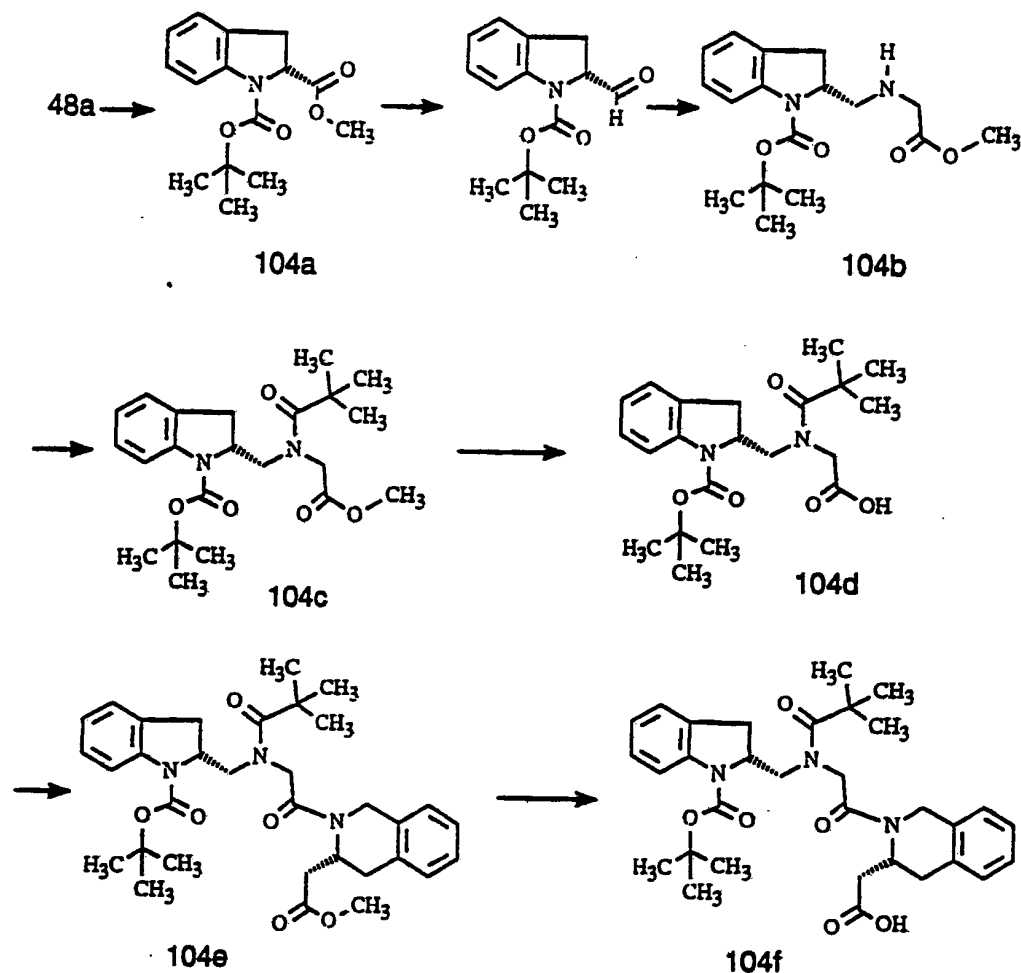


**103a** Methyl (3R)-2-{N-phenethyl-N-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetate.

This was prepared from 90b and 85c on a 0.48 mmol scale following the method described for 1d. The product was isolated in 85% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

**103b** (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butoxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetic acid.

This was prepared from 103a on a 0.41 mmol scale following the method described for 1f. The product was isolated in 74% yield (196 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A  $t_R=22.4'$  >98%Mass spec (FAB)  $m/e=648$   $[M+H]^+$ **EXAMPLE 104****104a Methyl (2R)-1-tert-butyloxycarbonyl-2,3-dihydroindole-2-carboxylate.**

To a stirred solution of 48a (1.05 g, 4 mmol) and 4-dimethylaminopyridine (50 mg, 0.4 mmol) in  $\text{CH}_2\text{Cl}_2$  (20 mL) and MeOH (10 mL) was added WSCD.HCl (1.54 g, 8 mmol). The mixture was stirred at room temperature for 3 hrs. and then concentrated *in vacuo*. The residue was partitioned between EtOAc and  $\text{H}_2\text{O}$ , and the organic phase was washed with 10%  $\text{KHSO}_4$ , satd.  $\text{KHCO}_3$  and brine, filtered (Whatman<sup>®</sup> 1PS phase separator), and concentrated *in vacuo* to give the title compound (0.89 g, 80%) as an oil which was used without further purification.

**104b Methyl N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycinate.**

This was prepared from 104a and GlyOMe on a 3.2 mmol scale following the method described for 31a. The product was isolated in 33% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 then 40:60 v/v).

R<sub>f</sub> (EtOAc:hexane 25:75 v/v) 0.08

**104c Methyl N-pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycinate.**

To an ice-cold stirred solution of 104b (70 mg, 0.22 mmol) and diisopropylethylamine (0.15 mL, 0.9 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added pivaloyl chloride (80 mL, 0.66 mmol). The mixture was stirred at 0°C for 2 hrs. and then concentrated *in vacuo*. The residue was partitioned between EtOAc and H<sub>2</sub>O, and the organic phase was washed with 10% KHSO<sub>4</sub>, satd. KHCO<sub>3</sub> and brine, filtered (Whatman<sup>®</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v) to give the title compound (67 mg, 75%).

R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.34

**104d N-Pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycine.**

This was prepared from 104c on a 0.17 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**104e Methyl (3R)-2-{N-pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 104d and 1c on a 0.17 mmol scale following the method described for 1d. The product was isolated in 65% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.25

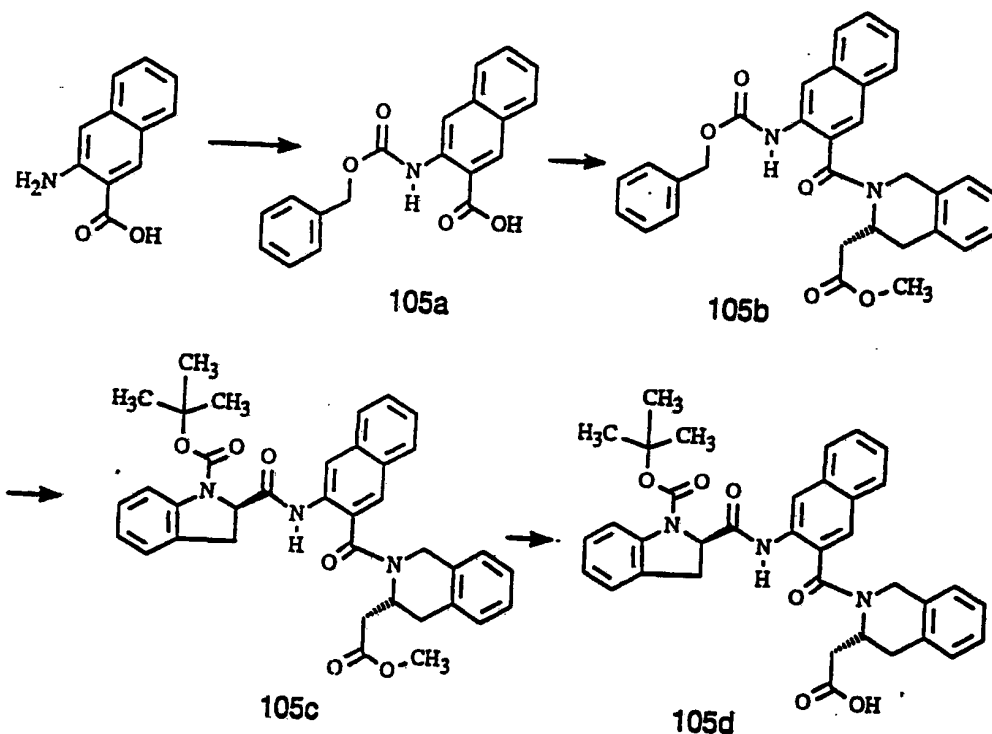
**104f (3R)-2-{N-pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 104e on a 0.11 mmol scale following the method described for 1f. The product was isolated in 50% yield (31 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:1 v/v/v).

HPLC System A t<sub>R</sub>=18.0' >98%

Mass spec (FAB) m/e=564 [M+H]<sup>+</sup>

## EXAMPLE 105

**105a 3-(Benzyloxycarbonylamino)-naphthalene-2-carboxylic acid.**

To a stirred suspension of 3-aminonaphthalene-2-carboxylic acid (4.22 g, 22.5 mmol) in H<sub>2</sub>O (37.5 mL) was added 5N NaOH (4.95 mL, 24.8 mmol). The resulting solution was cooled in ice then treated alternately with benzyl chloroformate (4 mL, 28.3 mmol) and 2N NaOH (14 mL, 28 mmol) in five equal portions. Acetonitrile (50 mL) was added and the mixture was stirred at room temperature overnight then concentrated *in vacuo*. The residue was partitioned between EtOAc and 0.3M KHSO<sub>4</sub>, and the organic phase was washed with 0.3M KHSO<sub>4</sub>, H<sub>2</sub>O and brine, filtered (Whatman<sup>®</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by recrystallisation from acetonitrile to give the title compound (3.09 g, 42%).

**105b Methyl (3R)-2-{3-(benzyloxycarbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 105a and 1c on a 0.78 mmol scale following the method described for 1d. The product was isolated in 76% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

**105c Methyl (3R)-2-{3-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-naphthalene-2-carboxyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 105b and 1c on a 0.59 mmol scale following the method described for 1d. The starting material 105b was deprotected prior to coupling by catalytic hydrogenolysis over 5% Pd-on-C in 1% v/v AcOH/MeOH as solvent for 90 min. The product was isolated in 66% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

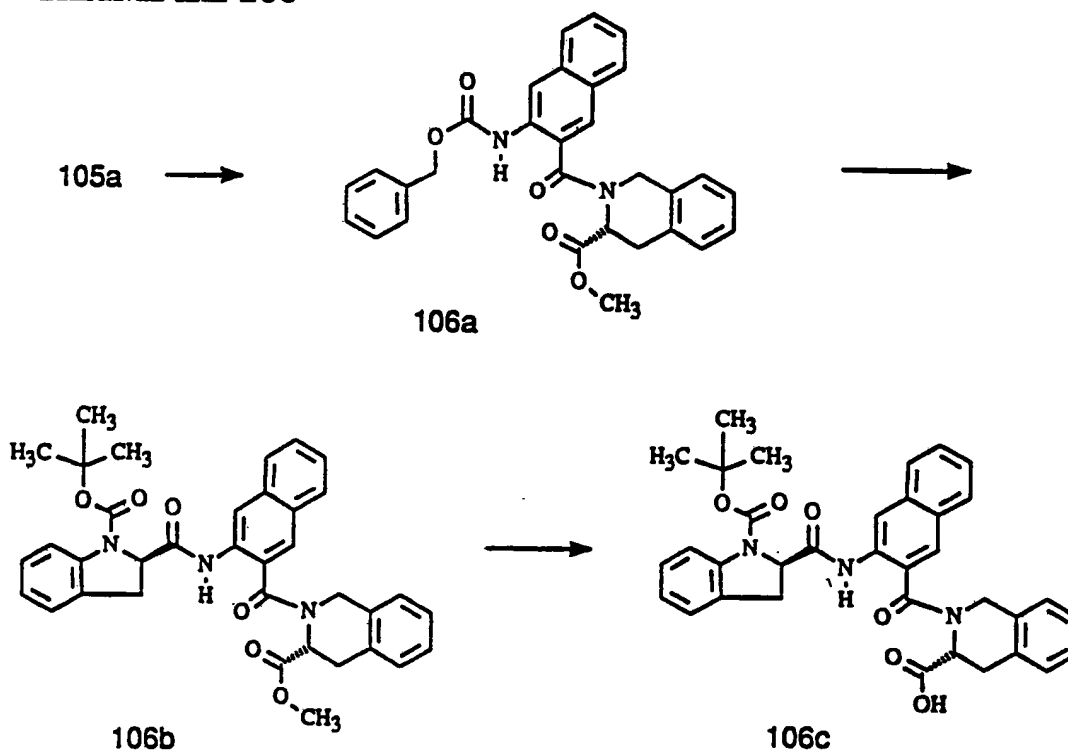
**105d (3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-naphthalene-2-carboxyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 105c on a 0.39 mmol scale following the method described for 1f. The product was isolated in 52% yield (123 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System B  $t_R$ =14.2' >95%

Mass spec (FAB)  $m/e$ =606 [M+H]<sup>+</sup>

## EXAMPLE 106



**106a Methyl (3R)-2-{3-(benzyloxycarbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 105a and 26a on a 1.22 mmol scale following the method described for 1d. The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**106b Methyl (3R)-2-{3-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

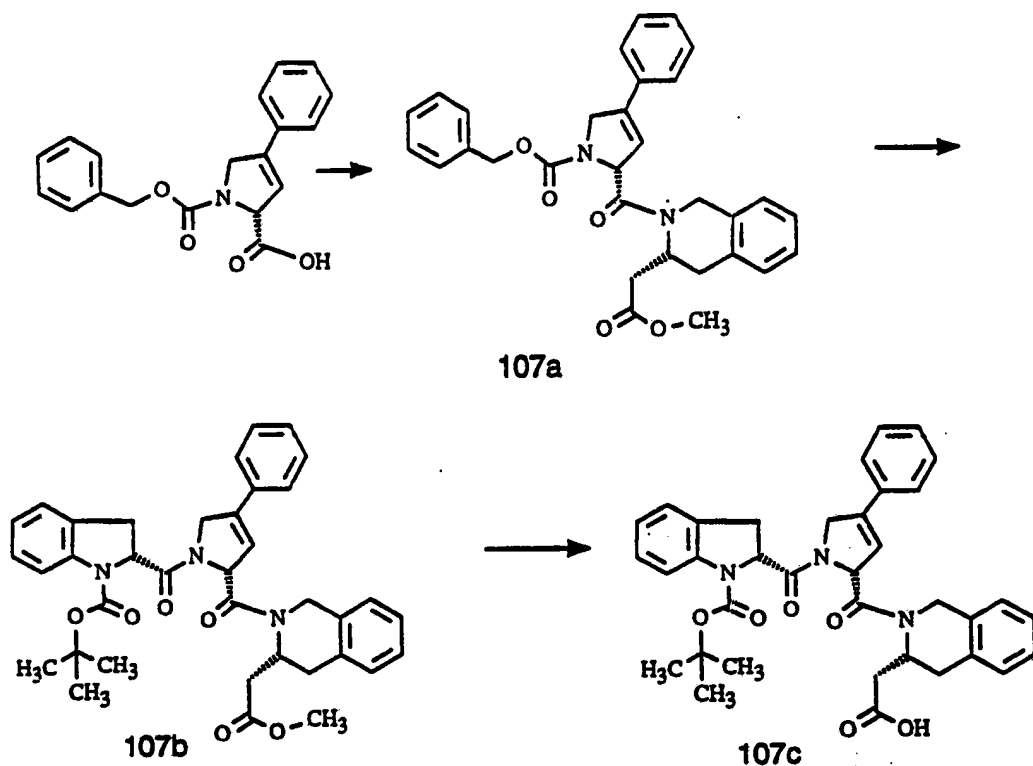
This was prepared from 106a and 48a on a 0.78 mmol scale following the method described for 105c. The product was isolated in 47% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**106c (3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 106b on a 0.38 mmol scale following the method described for 1f. The product was isolated in 70% yield (159 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:1 v/v/v).

HPLC System B  $t_R$  = 14.1' >95%

Mass spec (FAB)  $m/e$  = 592  $[M+H]^+$

**EXAMPLE 107**

**107a** Methyl (3R)-2-((2R)-1-benzyloxycarbonyl-4-phenyl-2,5-dihydropyrrole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c on a 1.3 mmol scale following the method described for 1d using (2R)-1-benzyloxycarbonyl-4-phenyl-2,5-dihydropyrrole-2-carboxylic acid (J. Krapcho *et al.*, *J. Med. Chem.*, 31, 1148, 1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 48% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v).

**107b** Methyl (3R)-2-((2R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-2,5-dihydropyrrole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 107a and 48a on a 0.63 mmol scale following the method described for 1d. The starting material 107a was deprotected prior to coupling by treatment with 45% HBr in AcOH for 90 min. The product was isolated in 27% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

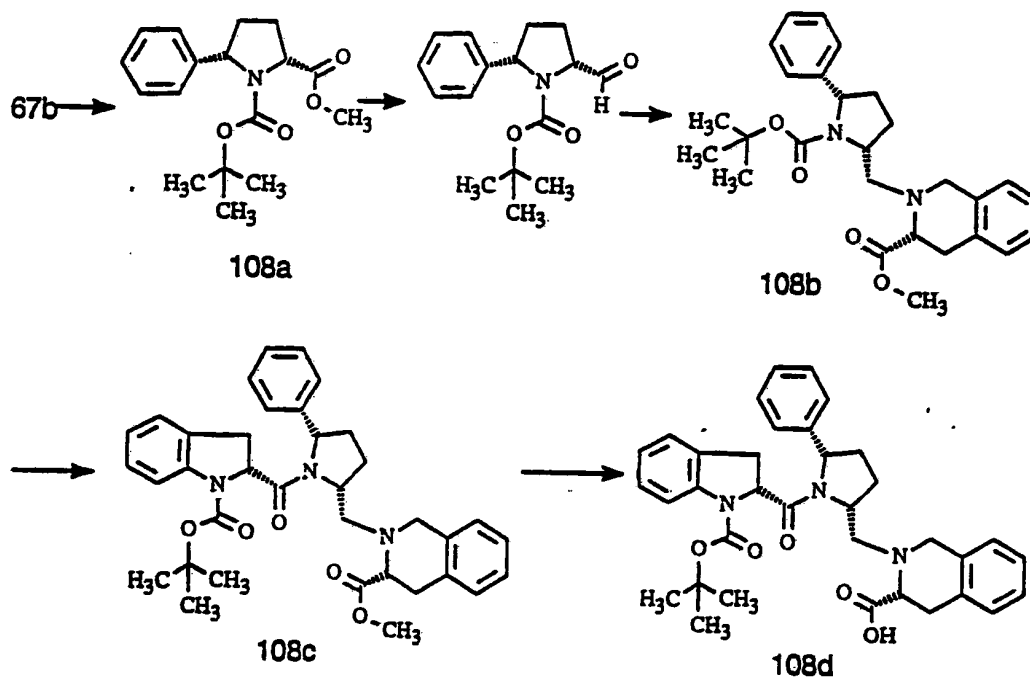
**107c (3R)-2-((2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-2,5-dihydropyrrole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 107b on a 0.17 mmol scale following the method described for 1f. The product was isolated in 40% yield (41 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 40:60:2 v/v/v).

HPLC System B  $t_R$ =14.4' >95%

Mass spec (FAB)  $m/e$ =508 [M+H]<sup>+</sup>

### EXAMPLE 108



**108a Methyl (2R,5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carboxylate.**

This was prepared from 67b on a 1.0 mmol scale following the method described for 104a. The product was used without purification, assuming a yield of 100%.

**108b Methyl (3R)-2-((2R,5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-methyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 108a and 26a on a 1.0 mmol scale following the method described for 31a. The intermediate aldehyde was isolated in 58% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v). The product was



isolated in 50% yield (based on a 0.58 mmol scale for the second part of the preparation) after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

**108c Methyl (3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-methyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

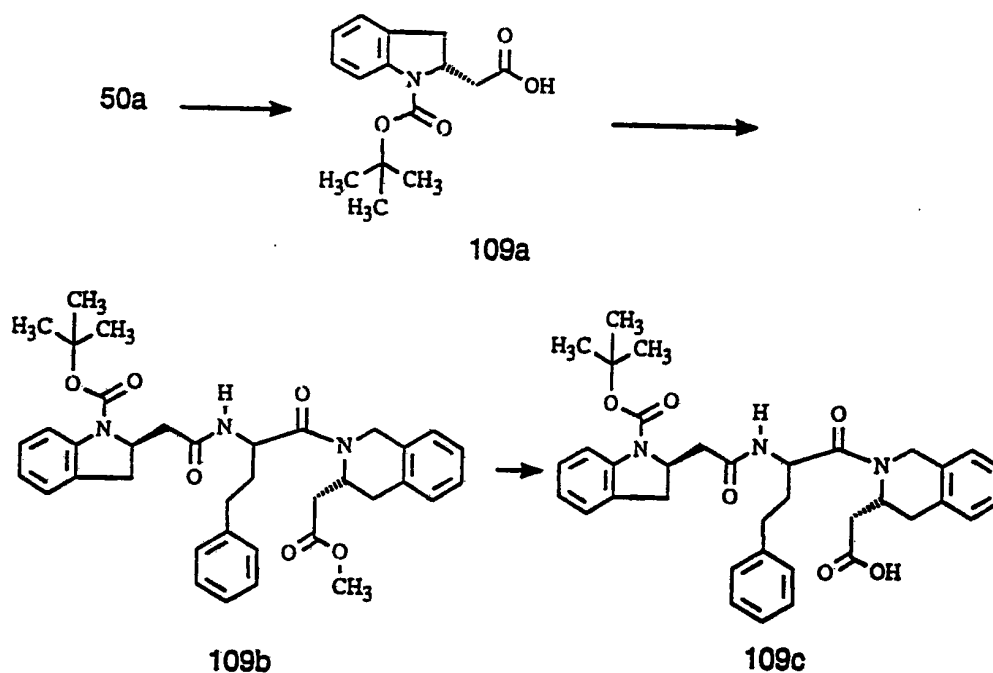
This was prepared from 108b and 48a on a 0.29 mmol scale following the method described for 1d. The starting material 107a was deprotected prior to coupling by treatment with 4*N* HCl in dioxan for 90 min. The product was isolated in 93% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

**108d (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-methyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 108c on a 0.27 mmol scale following the method described for 1f. The product was isolated in 71% yield (111 mg) after flash chromatography on silica gel (eluant CHCl<sub>3</sub>:MeOH:AcOH 100:3:2 v/v/v).

HPLC System A  $t_R$ =18.2' >99%

Mass spec (FAB)  $m/e$ =582 [M+H]<sup>+</sup>

**EXAMPLE 109****109a (2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-acetic acid.**

This was prepared from 50a on a 0.25 mmol scale following the method described for 1f. The product was used without further purification, assuming a yield of 100%.

**109b Methyl (3R)-2-((2S)-2-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-acetylamino)-4-phenylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 13a and 109a on a 0.25 mmol scale following the method described for 32d. The product was isolated in 90% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 25:75:2 v/v/v).

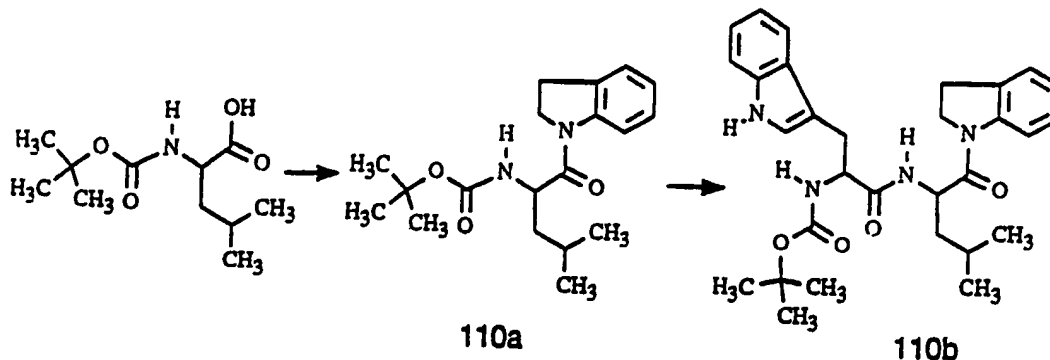
**109c (3R)-2-((2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-acetylamino)-4-phenylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 109b on a 0.22 mmol scale following the method described for 1f. The product was isolated in 80% yield (109 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 40:60:2 v/v/v).

HPLC System B  $t_R=15.2'$  >98%

Mass spec (FAB)  $m/e=612$   $[M+H]^+$

## EXAMPLE 110

**110a 1-(*tert*-Butyloxycarbonyl-leucyl)-2,3-dihydroindole.**

To an ice-cold stirred solution of BOC-Leu (4.62 g, 20 mmol) and pentafluorophenol (4.42 g, 24 mmol) in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added WSCD.HCl (7.65 g, 40 mmol). The mixture was stirred at  $0^\circ\text{C}$  for 1 hr., then indoline (4.0 mL, 36 mmol) and 4-dimethylaminopyridine were added and the mixture was stirred at room temperature for 4 days then concentrated *in vacuo*. The residue was partitioned between EtOAc and 0.3M  $\text{KHSO}_4$ , and the organic phase was washed with 0.3M  $\text{KHSO}_4$ ,  $\text{H}_2\text{O}$  and brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 10:90 v/v) to give the title product (3.41 g, 51%).

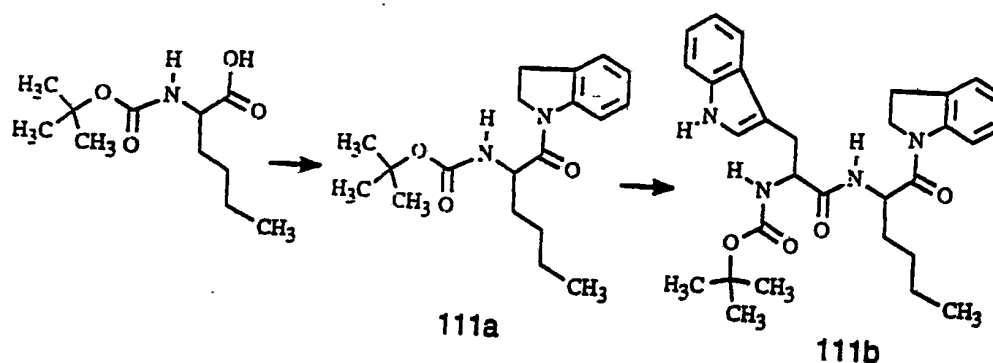
**110b 1-(*tert*-Butyloxycarbonyl-tryptophanyl-leucyl)-2,3-dihydroindole.**

This was prepared from 110a on a 1.08 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 79% yield (445 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 then 50:50 v/v).

HPLC System A  $t_R=17.5'$  >95%

AAA Peptide content=99%

Mass spec (FAB)  $m/e=519$   $[\text{M}+\text{H}]^+$

**EXAMPLE 111****111a 1-((2S)-2-(tert-Butyloxycarbonylamino)-hexanoyl)-2,3-dihydroindole.**

This was prepared from BOC-aminohexanoic acid on a 8.4 mmol scale following the method described for 110a. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

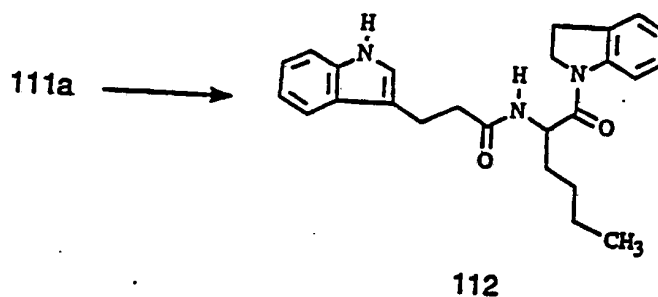
**111b 1-((2S)-2-(tert-Butyloxycarbonyl-tryptophanyl-amino)-hexanoyl)-2,3-dihydroindole.**

This was prepared from 111a on a 0.88 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 66% yield (300 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R$ =14.8' >99%

AAA Peptide content=93%

Mass spec (FAB)  $m/e$ =519  $[M+H]^+$

**EXAMPLE 112**

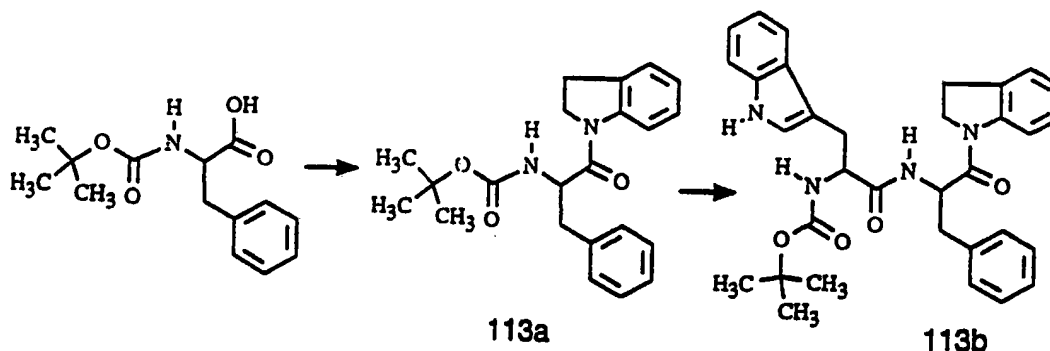
**112 1-((2S)-2-(3-Indole-3-propanoylamino)-hexanoyl)-2,3-dihydroindole.**

This was prepared from 111a on a 0.63 mmol scale following the method described for 32d using 3-indole-3-propanoic acid instead of indoleacetic acid. The product was isolated in 96% yield (244 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 30:70:2 then 40:60:2 v/v/v).

HPLC System A  $t_R$ =11.6' >95%

AAA Peptide content=88%

Mass spec (FAB)  $m/e$ =404  $[M+H]^+$

**EXAMPLE 113****113a 1-((tert-Butyloxycarbonyl-phenylalanyl))-2,3-dihydroindole.**

This was prepared from BOC-Phe on a 0.75 mmol scale following the method described for 110a. The product was isolated in 60% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

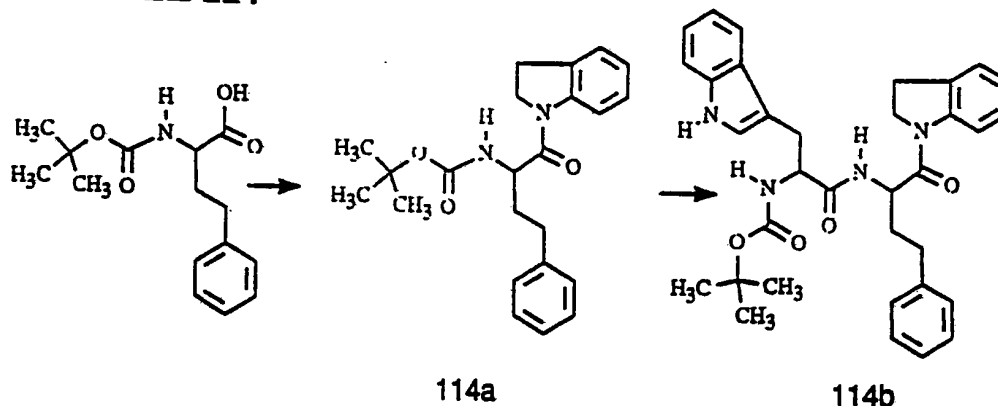
**113b 1-((tert-Butyloxycarbonyl-tryptophanyl-phenylalanyl))-2,3-dihydroindole.**

This was prepared from 113a on a 0.45 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 61% yield (152 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

HPLC System A  $t_R$ =18.9' >95%

AAA Peptide content=90%

Mass spec (FAB)  $m/e$ =553  $[M+H]^+$

**EXAMPLE 114**

**114a 1-((2S)-2-(*tert*-Butyloxycarbonylamino)-4-phenylbutanoyl)-2,3-dihydroindole.**

This was prepared from BOC-homophenylalanine on a 2.25 mmol scale following the method described for 110a. The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 18:82 v/v).

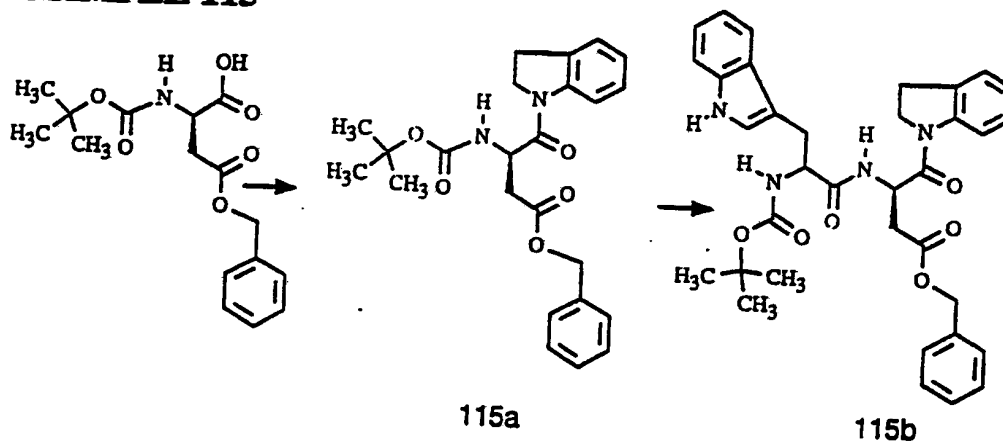
**114b 1-((2S)-2-(*tert*-Butyloxycarbonyl-tryptophanyl-amino)-4-phenylbutanoyl)-2,3-dihydroindole.**

This was prepared from 114a on a 0.48 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 73% yield (197 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

HPLC System A  $t_R$ =20.2' >98%

AAA Peptide content=100%

Mass spec (FAB)  $m/e$ =567  $[M+H]^+$

**EXAMPLE 115**

**115a 1-(*tert*-Butyloxycarbonyl-( $\beta$ -O-benzyl)-D-aspartyl)-2,3-dihydroindole.**

This was prepared from BOC-D-Asp(OBzl)OH on a 4.0 mmol scale following the method described for 110a. The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

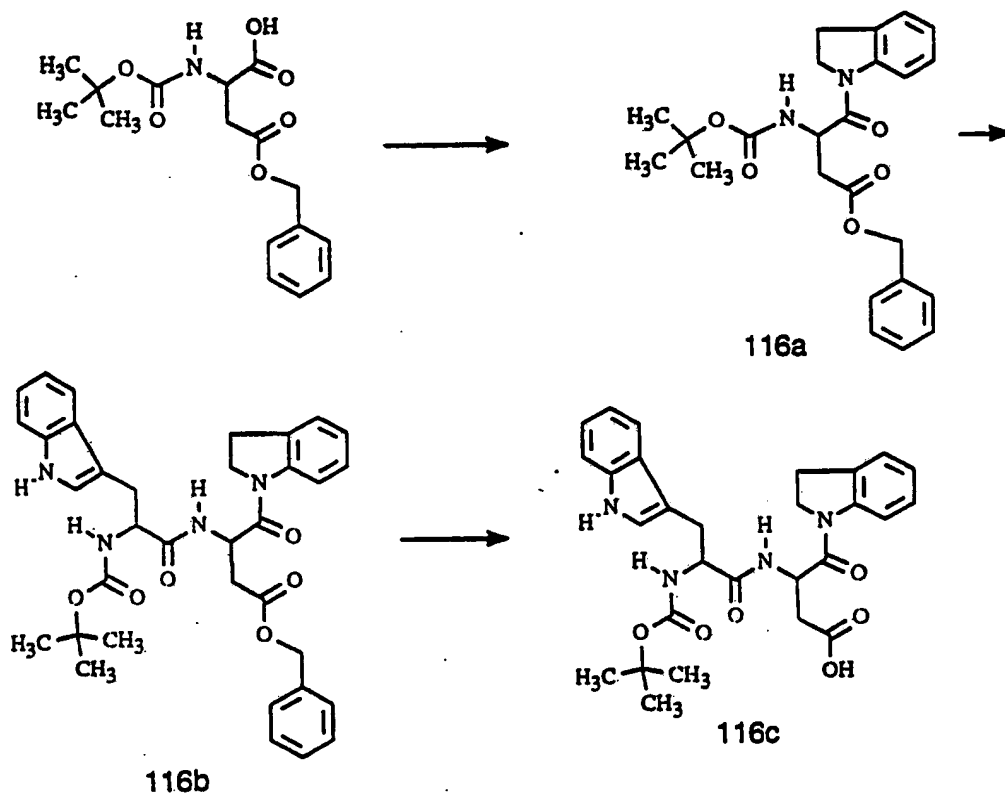
**115b 1-(*tert*-Butyloxycarbonyl-tryptophanyl-( $\beta$ -O-benzyl)-D-aspartyl)-2,3-dihydroindole.**

This was prepared from 115a on a 1.18 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 45% yield (325 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

HPLC System A  $t_R$ =17.2' >99%

AAA Peptide content=91%

Mass spec (FAB)  $m/e$ =611 [M+H]<sup>+</sup>

**EXAMPLE 116**

**116a 1-{*tert*-Butyloxycarbonyl-( $\beta$ -O-benzyl)-aspartyl}-2,3-dihydroindole.**

This was prepared from BOC-Asp(OBzl)OH on a 4.0 mmol scale following the method described for 110a. The product was isolated in 57% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

**116b 1-{*tert*-Butyloxycarbonyl-tryptophanyl-( $\beta$ -O-benzyl)-aspartyl}-2,3-dihydroindole.**

This was prepared from 116a on a 1.18 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 55% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

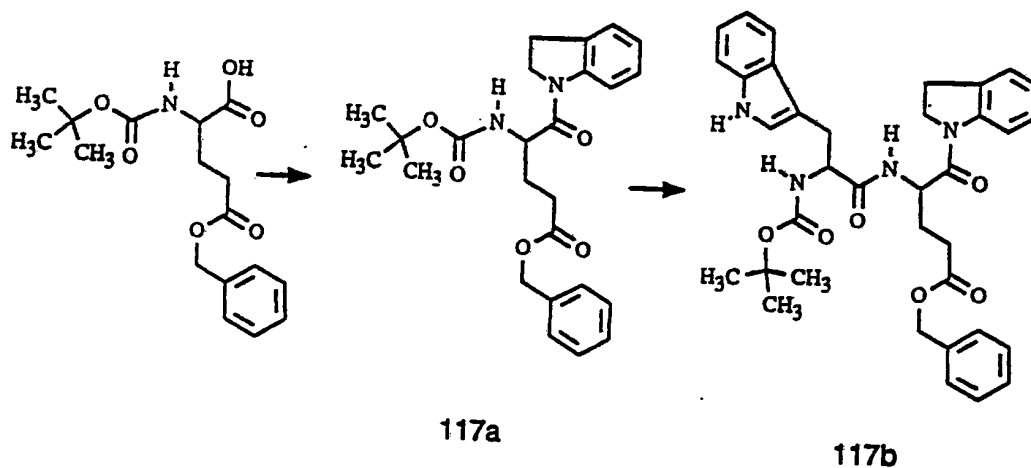
**116c 1-{*tert*-Butyloxycarbonyl-tryptophanyl-aspartyl}-2,3-dihydroindole.**

This was prepared from 116b on a 0.32 mmol scale following the method described for 1f. The product was isolated in 73% yield (122 mg) without purification.

HPLC System A  $t_R=8.5'$  >99%

AAA Peptide content=91%

Mass spec (FAB)  $m/e=521$   $[M+H]^+$

**EXAMPLE 117****117a 1-{*tert*-Butyloxycarbonyl-( $\gamma$ -O-benzyl)-glutamyl}-2,3-dihydroindole.**

This was prepared from BOC-Glu(OBzl)OH on a 4.0 mmol scale following the method described for 110a. The product was isolated in 45% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).



**117b**                    **1-(*tert*-Butyloxycarbonyl-tryptophanyl-( $\gamma$ -O-benzyl)-glutamyl)-2,3-dihydroindole.**

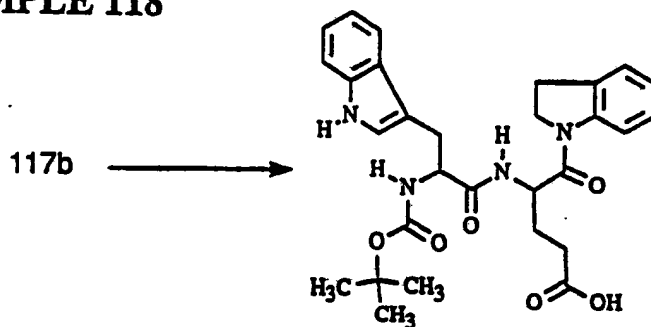
This was prepared from 117a on a 1.18 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 59% yield (437 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

HPLC System A  $t_R$ =17.9' >99%

AAA Peptide content=94%

Mass spec (FAB)  $m/e$ =625  $[M+H]^+$

**EXAMPLE 118**



**118**

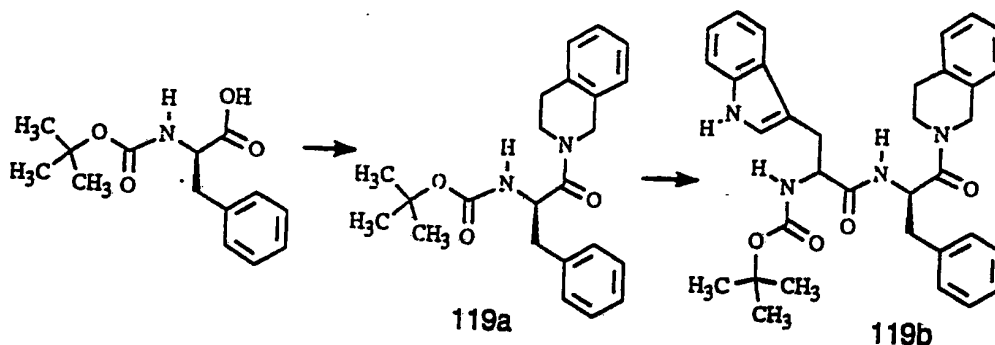
**118 1-(*tert*-Butyloxycarbonyl-tryptophanyl-glutamyl)-2,3-dihydroindole.**

This was prepared from 117b on a 0.35 mmol scale following the method described for 1f. The product was isolated in 70% yield (132 mg) after flash chromatography on silica gel (eluant EtOAc then EtOAc:AcOH 100:1 v/v).

HPLC System A  $t_R$ =9.1' >98%

AAA Peptide content=87%

Mass spec (FAB)  $m/e$ =535  $[M+H]^+$

**EXAMPLE 119****119a 2-{*tert*-Butyloxycarbonyl-D-phenylalanyl}-1,2,3,4-tetrahydroisoquinoline.**

This was prepared from BOC-D-Phe and tetrahydroisoquinoline on a 0.75 mmol scale following the method described for 110a. The product was isolated in 77% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

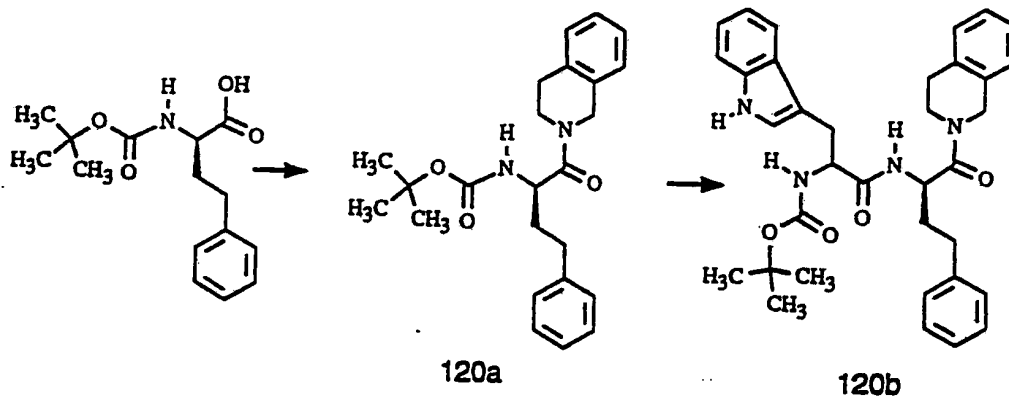
**119b 2-{*tert*-Butyloxycarbonyl-tryptophanyl-D-phenylalanyl}-1,2,3,4-tetrahydroisoquinoline.**

This was prepared from 119a on a 0.58 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 72% yield (237 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

HPLC System A  $t_R$ =18.3' >98%

AAA Peptide content=84%

Mass spec (FAB)  $m/e$ =567  $[M+H]^+$

**EXAMPLE 120**

**120a**      2-[(2R)-2-(*tert*-Butyloxycarbonylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline.

This was prepared from BOC-D-homophenylalanine and tetrahydroisoquinoline on a 0.72 mmol scale following the method described for 110a. The product was isolated in 85% yield and used without further purification.

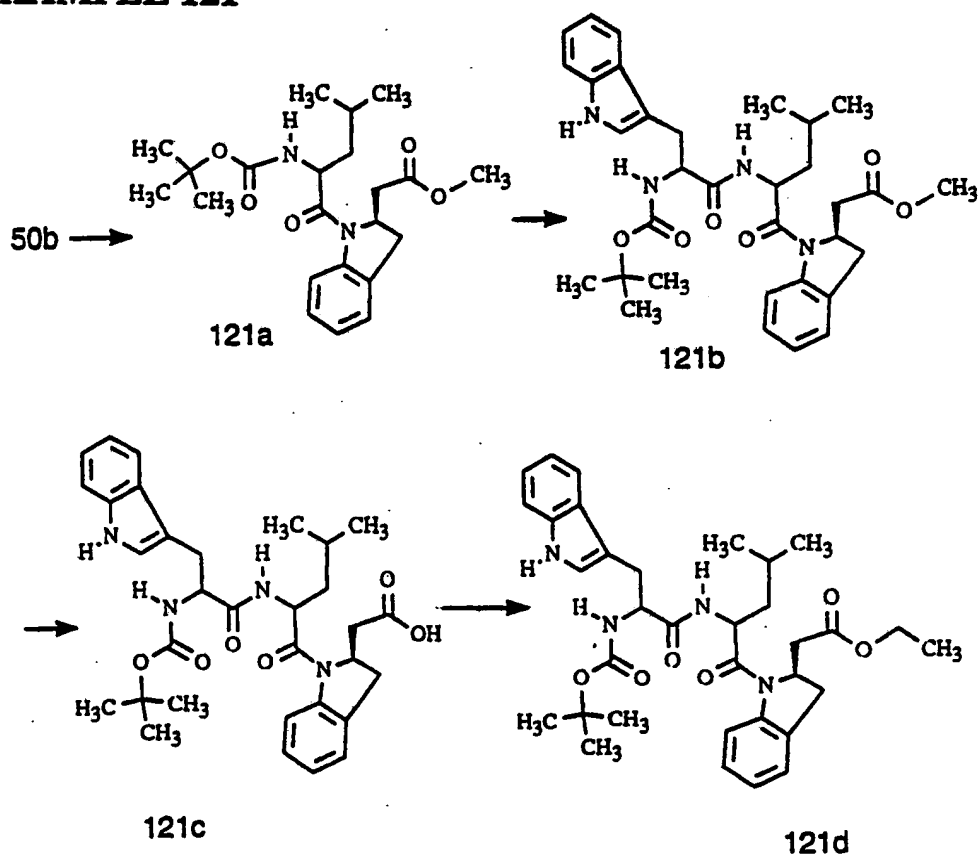
**120b**      2-[(2R)-2-(*tert*-Butyloxycarbonyl-tryptophanyl-amino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline.

This was prepared from 120a on a 0.67 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 69% yield (270 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:2 v/v/v).

HPLC System A  $t_R$ =16.3' >99%

AAA Peptide content=97%

**EXAMPLE 121**



**121a Methyl (2R)-1-(*tert*-butyloxycarbonyl-leucyl)-2,3-dihydroindole-2-acetate.**

This was prepared from BOC-Leu and 50b on a 0.6 mmol scale following the method described for 1d. The product was isolated in 38% yield after flash chromatography on silica gel (eluant EtOAc:hexane 14:86 v/v).

**121b Methyl (2R)-1-(*tert*-butyloxycarbonyl-tryptophanyl-leucyl)-2,3-dihydroindole-2-acetate.**

This was prepared from 121a on a 0.67 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 94% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).

**121c (2R)-1-(*tert*-Butyloxycarbonyl-tryptophanyl-leucyl)-2,3-dihydroindole-2-acetic acid.**

This was prepared from 121b on a 0.16 mmol scale following the method described for 1f. The product was isolated in 85% yield and used without further purification.

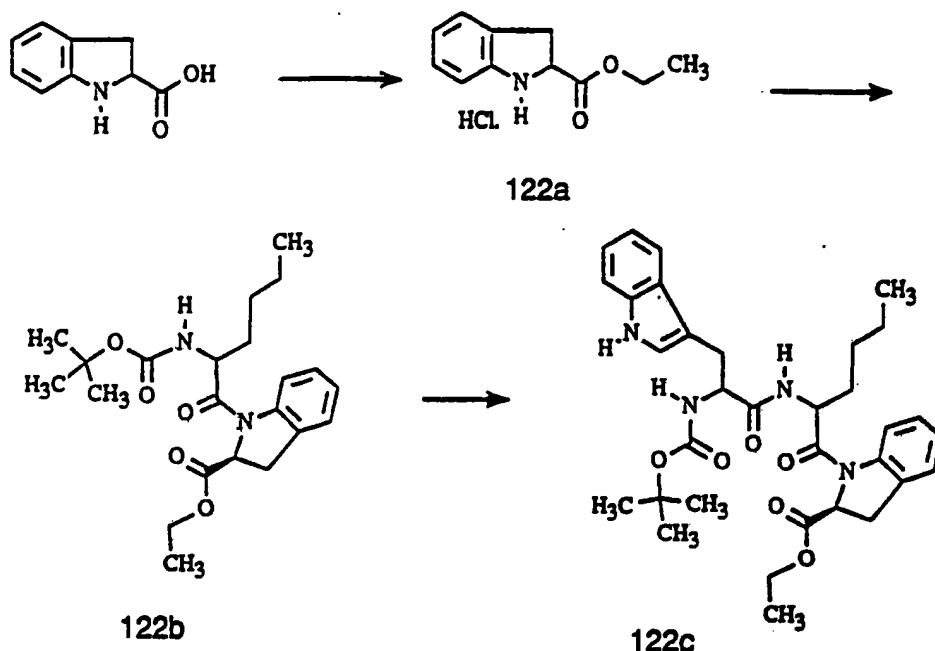
**121d Ethyl (2R)-1-(*tert*-butyloxycarbonyl-tryptophanyl-leucyl)-2,3-dihydroindole-2-acetate.**

This was prepared from 121c on a 0.12 mmol scale following the method described for 104a using EtOH instead of MeOH. The product was isolated in 82% yield (60 mg) after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

HPLC System B  $t_R$ =17.3' >98%

AAA Peptide content=86%

Mass spec (FAB)  $m/e$ =605  $[M+H]^+$

**EXAMPLE 122****122a Ethyl (2RS)-2,3-dihydroindole-2-carboxylate hydrochloride.**

This was prepared from (RS)-indoline-2-carboxylic acid on a 5.0 mmol scale following the method described for 26a using EtOH instead of MeOH. The product was isolated in 96% yield and used without further purification.

**122b Ethyl (2RS)-1-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-2,3-dihydroindole-2-carboxylate.**

This was prepared from 122a and BOC-aminohexanoic acid on a 6.0 mmol scale following the method described for 1d. The product was isolated in 62% yield after flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

**122c Ethyl (2S)-1-((2S)-2-(*tert*-butyloxycarbonyl-tryptophanyl-amino)-hexanoyl)-2,3-dihydroindole-2-carboxylate.**

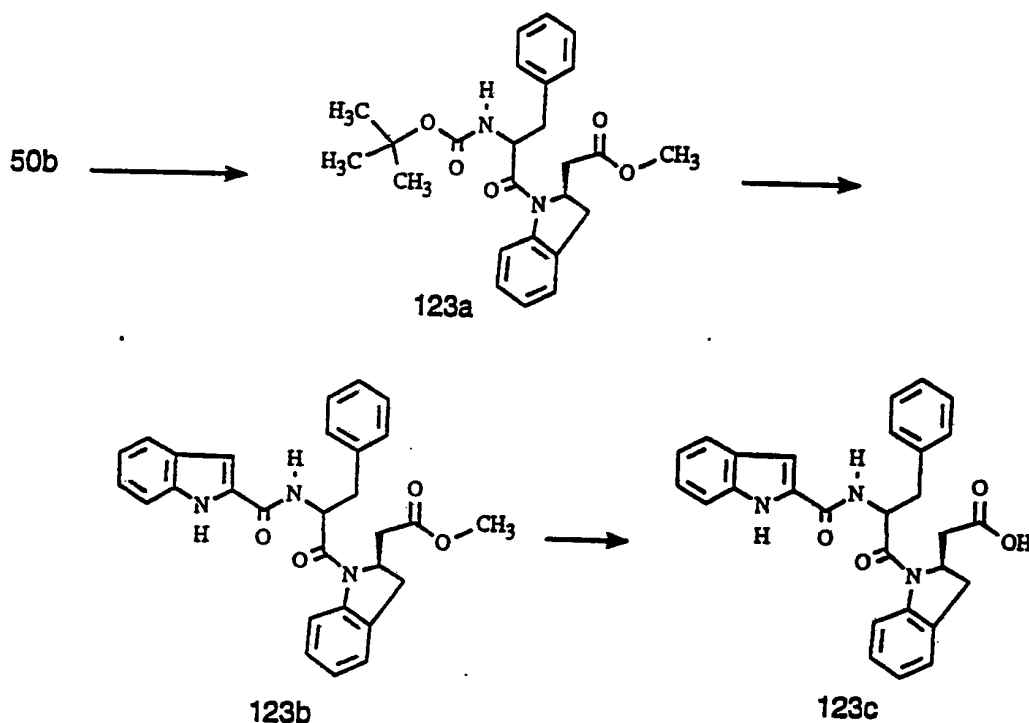
This was prepared from 122b on a 1.88 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 20% yield (220 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 28:72:2 v/v/v). The (2R)-indoline epimer was separated at this stage (43% yield).

HPLC System B  $t_R=16.6'$  >98%

AAA Peptide content=90%

Mass spec (FAB)  $m/e=591$   $[M+H]^+$

### EXAMPLE 123



**123a** Methyl (2R)-1-{*tert*-butoxycarbonyl-phenylalanyl}-2,3-dihydroindole-2-acetate.

This was prepared from BOC-Phe and 50b on a 0.52 mmol scale following the method described for 1d. The product was isolated in 45% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 15:85 v/v).

**123b** Methyl (2R)-1-{indole-2-carboxyl-phenylalanyl}-2,3-dihydroindole-2-acetate.

The compound 123a was deprotected on a 0.23 mmol scale following the method described for 1c to give methyl (2R)-1-phenylalanyl-2,3-dihydroindole-2-acetate hydrochloride which was then treated with indole-2-carboxyl chloride in the following manner.

To a stirred suspension of indole-2-carboxylic acid dicyclohexylamine salt (103 mg, 0.30 mmol) in  $CH_2Cl_2$  (15 mL) was added pyridine (32.3  $\mu$ L, 0.4 mmol) and then  $SOCl_2$

(180  $\mu$ L of 2M solution in  $\text{CH}_2\text{Cl}_2$ , 0.36 mmol). The mixture was stirred at room temperature for 1 min., then the methyl (2R)-1-phenylalanyl-2,3-dihydroindole-2-acetate hydrochloride and 4-dimethylaminopyridine (25 mg, 0.21 mmol) were added. The mixture was stirred at room temperature for 2 hr. and then concentrated *in vacuo*. The residue was partitioned between EtOAc and  $\text{H}_2\text{O}$ , and the organic phase was washed with 10%  $\text{KHSO}_4$ , satd.  $\text{KHCO}_3$  and brine, filtered (Whatman<sup>R</sup> 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v) to give the title compound (32 mg, 28%).

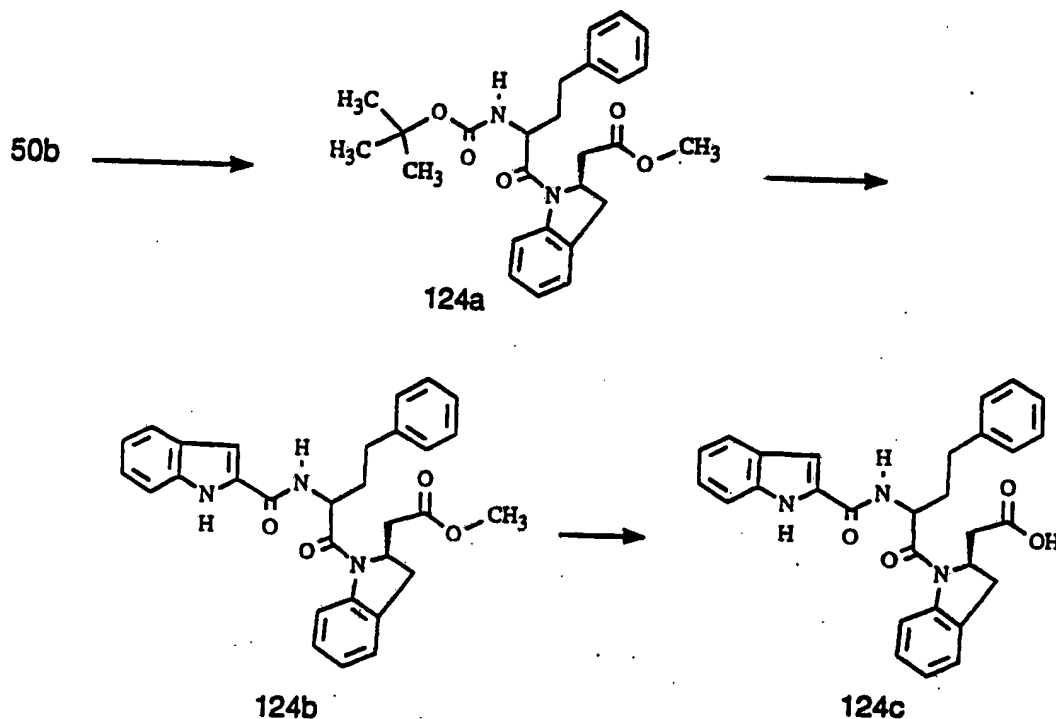
**123c (2R)-1-{Indole-2-carbonyl-phenylalanyl}-2,3-dihydroindole-2-acetic acid.**

This was prepared from 123b on a 0.066 mmol scale following the method described for 1f. The product was isolated in 90% yield (28 mg) without purification.

HPLC System B  $t_R$ =9.9' >90%

Mass spec (FAB)  $m/e$ =468  $[\text{M}+\text{H}]^+$

**EXAMPLE 124**



**124a Methyl (2R)-1-((2S)-2-(*tert*-butoxycarbonylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetate.**

This was prepared from BOC-homophenylalanine and racemic 50b on a 5.0 mmol scale following the method described for 1d. The product was isolated in 14% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 18:82 v/v) together with the (2R)-indoline epimer (isolated in 22% yield).

**124b Methyl (2R)-1-((2S)-2-(indole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetate.**

This was prepared from 124a on a 0.34 mmol scale following the method described for 123b. The semi-purified product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

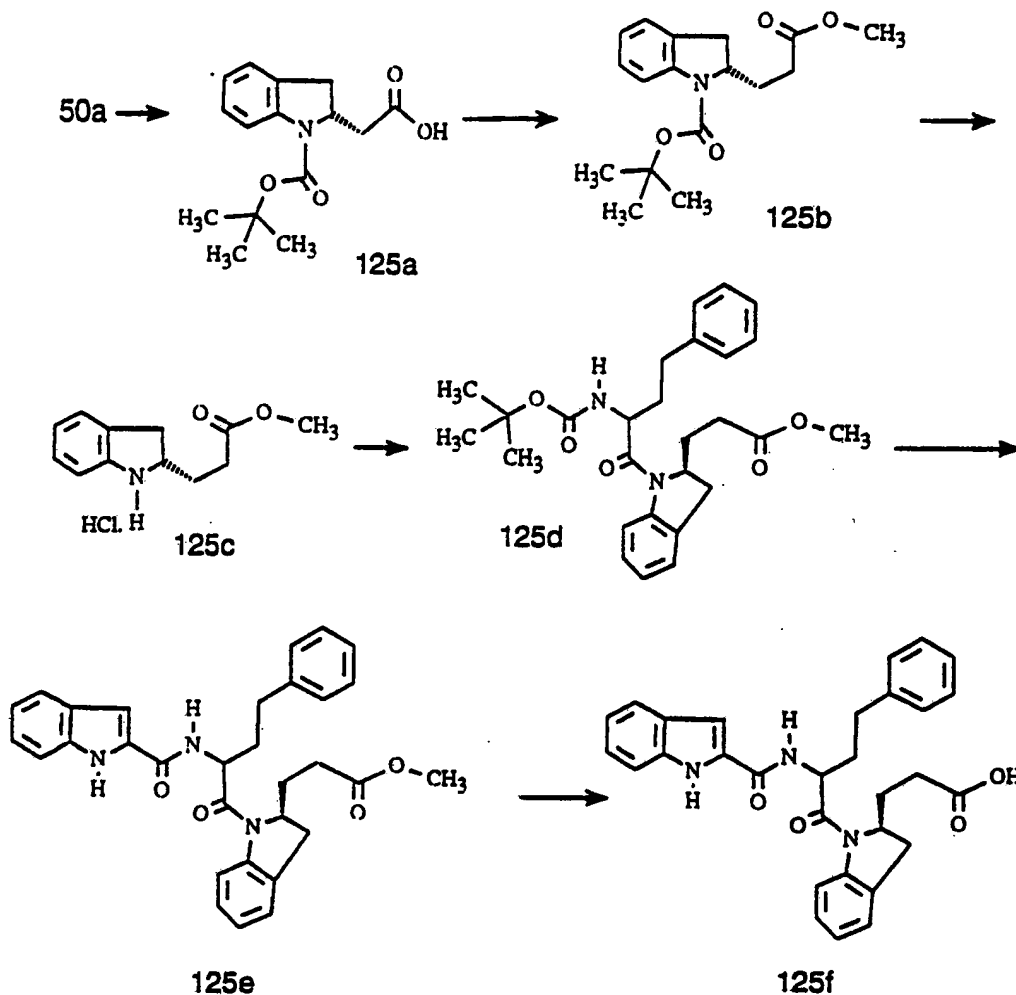
**124c (2R)-1-((2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetic acid.**

This was prepared from 124b on a 0.34 mmol scale following the method described for 1f. The product was isolated in 63% yield (196 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:2 v/v/v).

HPLC System A  $t_R$ =14.8' >95%

Mass spec (FAB)  $m/e$ =482 [M+H]<sup>+</sup>



**EXAMPLE 125****125a (2R)-1-*tert*-Butyloxycarbonyl-2.3-dihydroindole-2-acetic acid.**

This was prepared from 50a on a 3.4 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**125b Methyl 3-((2R)-1-*tert*-butyloxycarbonyl-2.3-dihydroindole-2-yl)-propanoate.**

This was prepared from 125a on a 3.4 mmol scale following the method described for 1b. The product was isolated in 44% yield after flash chromatography on silica gel (eluant EtOAc:hexane 12:88 v/v).

**125c Methyl 3-((2R)-2.3-dihydroindole-2-yl)-propanoate hydrochloride.**

This was prepared from 125b on a 1.0 mmol scale following the method described for 1c. The product was used without purification, assuming a yield of 100%.

**125d Methyl 3-((2R)-1-((2S)-2-(*tert*-butoxycarbonylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-yl)-propanoate.**

This was prepared from 125c and BOC-homophenylalanine on a 1.0 mmol scale following the method described for 1d. The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

**125e Methyl 3-((2R)-1-((2S)-2-(indole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-yl)-propanoate.**

This was prepared from 125d on a 0.43 mmol scale following the method described for 123b. The product was isolated in 41% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

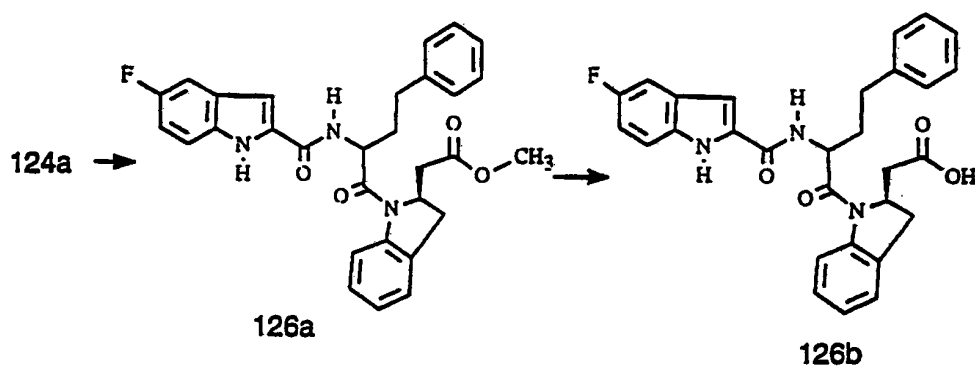
**125f 3-((2R)-1-((2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-yl)-propanoic acid.**

This was prepared from 125e on a 0.18 mmol scale following the method described for 1f. The product was isolated in 56% yield (43 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 40:60:2 v/v/v).

HPLC System B  $t_R$ =11.2' >80%

Mass spec (FAB)  $m/e$ =518  $[M+H]^+$

## EXAMPLE 126



**126a Methyl (2R)-1-((2S)-2-(5-fluoroindole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetate.**

This was prepared from 124a and 5-fluoroindole-2-carboxylic acid on a 0.20 mmol scale following the method described for 123b. The product was isolated in 54% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

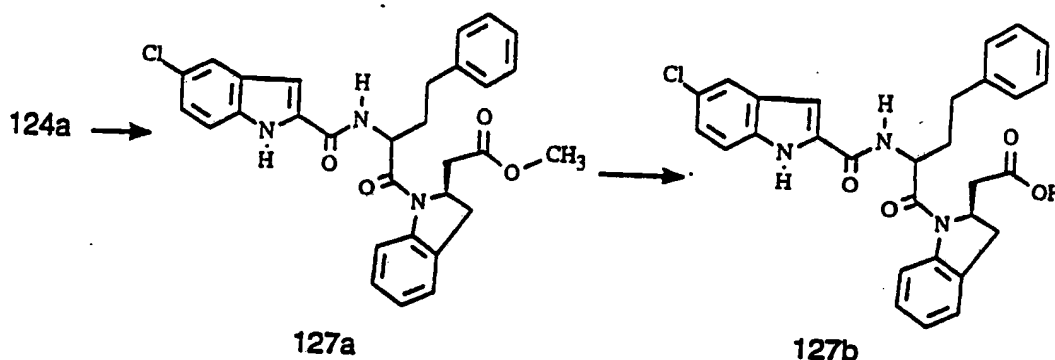
**126b** (2R)-1-((2S)-2-(5-Fluoroindole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetic acid.

This was prepared from 126a on a 0.11 mmol scale following the method described for 1f. The product was isolated in 73% yield (39 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:2 v/v/v).

HPLC System A  $t_R$ =14.2' >95%

Mass spec (FAB)  $m/e$ =500 [M+H]<sup>+</sup>

### EXAMPLE 127



**127a** Methyl (2R)-1-((2S)-2-(5-chloroindole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetic acid.

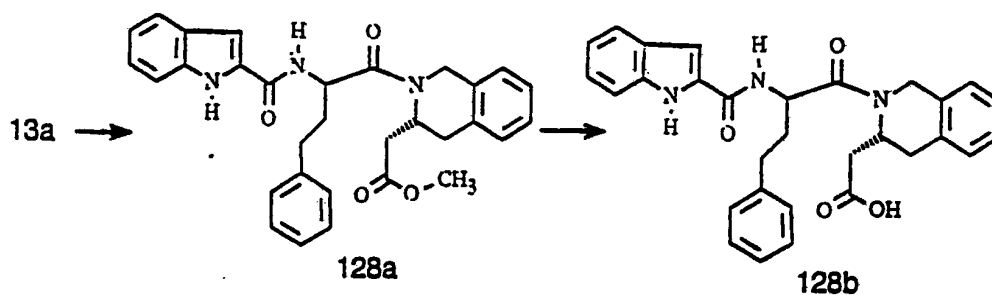
This was prepared from 124a and 5-chloroindole-2-carboxylic acid on a 0.20 mmol scale following the method described for 123b. The product was isolated in 52% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

**127b** (2R)-1-((2S)-2-(5-Chloroindole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetic acid.

This was prepared from 127a on a 0.10 mmol scale following the method described for 1f. The product was isolated in 78% yield (42 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:2 v/v/v).

HPLC System A  $t_R$ =16.0' >95%

Mass spec (FAB)  $m/e$ =511 [M+H]<sup>+</sup>

**EXAMPLE 128**

**128a** Methyl (3R)-2-[(2S)-2-(indole-2-carboxylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 13a on a 0.12 mmol scale following the method described for 123b. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

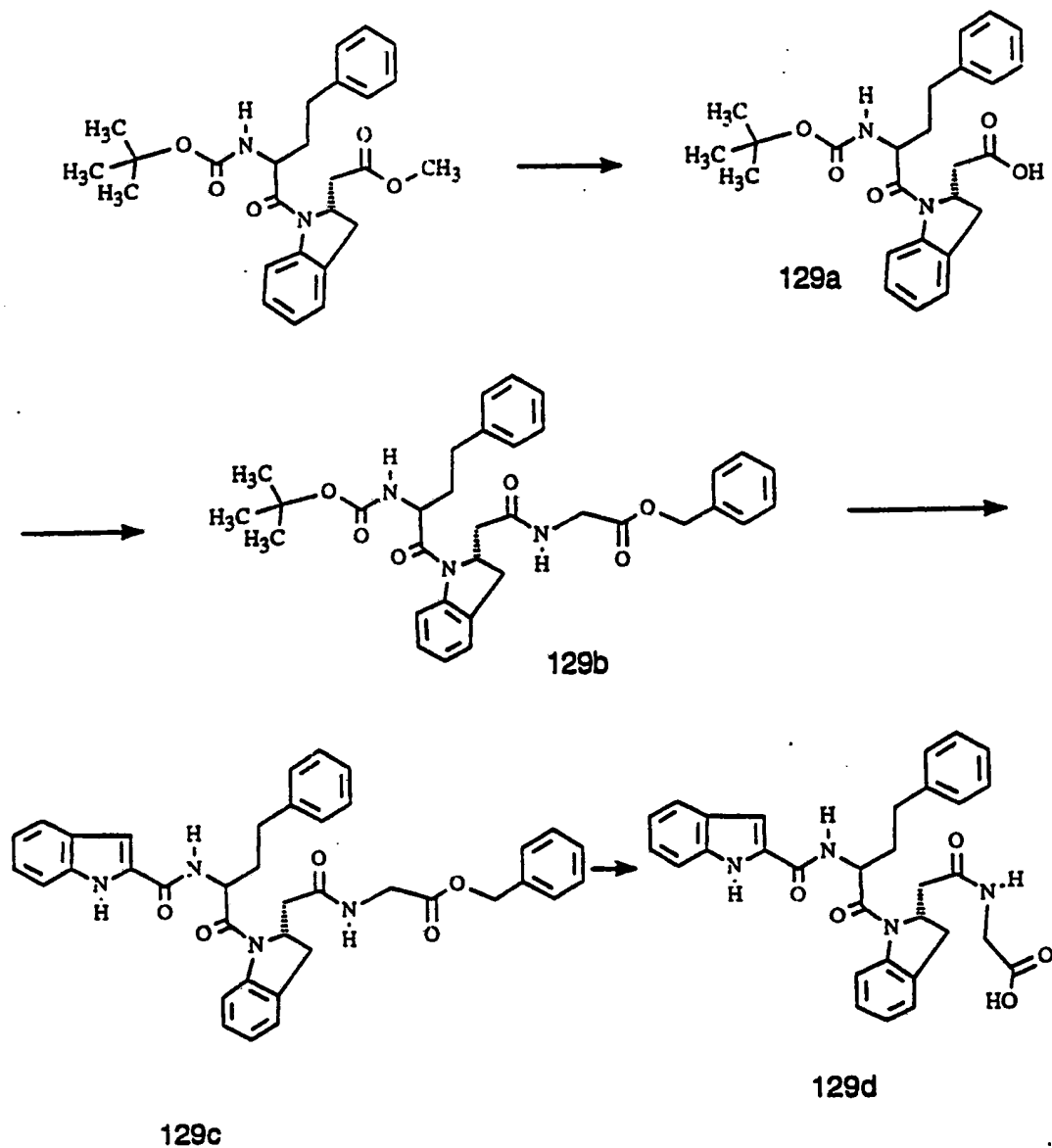
**128b** (3R)-2-[(2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 128a on a 0.09 mmol scale following the method described for 1f. The product was isolated in 66% yield (31 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A  $t_R$ =14.8' >99%

Mass spec (FAB)  $m/e$ =496  $[M+H]^+$

## EXAMPLE 129



**129a** (2S)-1-((2S)-2-(*tert*-Butyloxycarbonylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetic acid.

This was prepared from the (2S)-indoline epimer of 124a on a 0.68 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**129b** Benzyl N-{(2S)-1-[(2S)-2-(*tert*-butoxycarbonylamino)-4-phenylbutanoyl]-2,3-dihydroindole-2-acetyl}-glycinate.

This was prepared from 129a and GlyOBzl on a 0.68 mmol scale following the method described for 1d. The product was isolated in 53% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

**129c** Benzyl N-{(2S)-1-[(2S)-2-(indole-2-carboxylamino)-4-phenylbutanoyl]-2,3-dihydroindole-2-acetyl}-glycinate.

This was prepared from 129b and on a 0.36 mmol scale following the method described for 123b. The product was isolated in 45% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

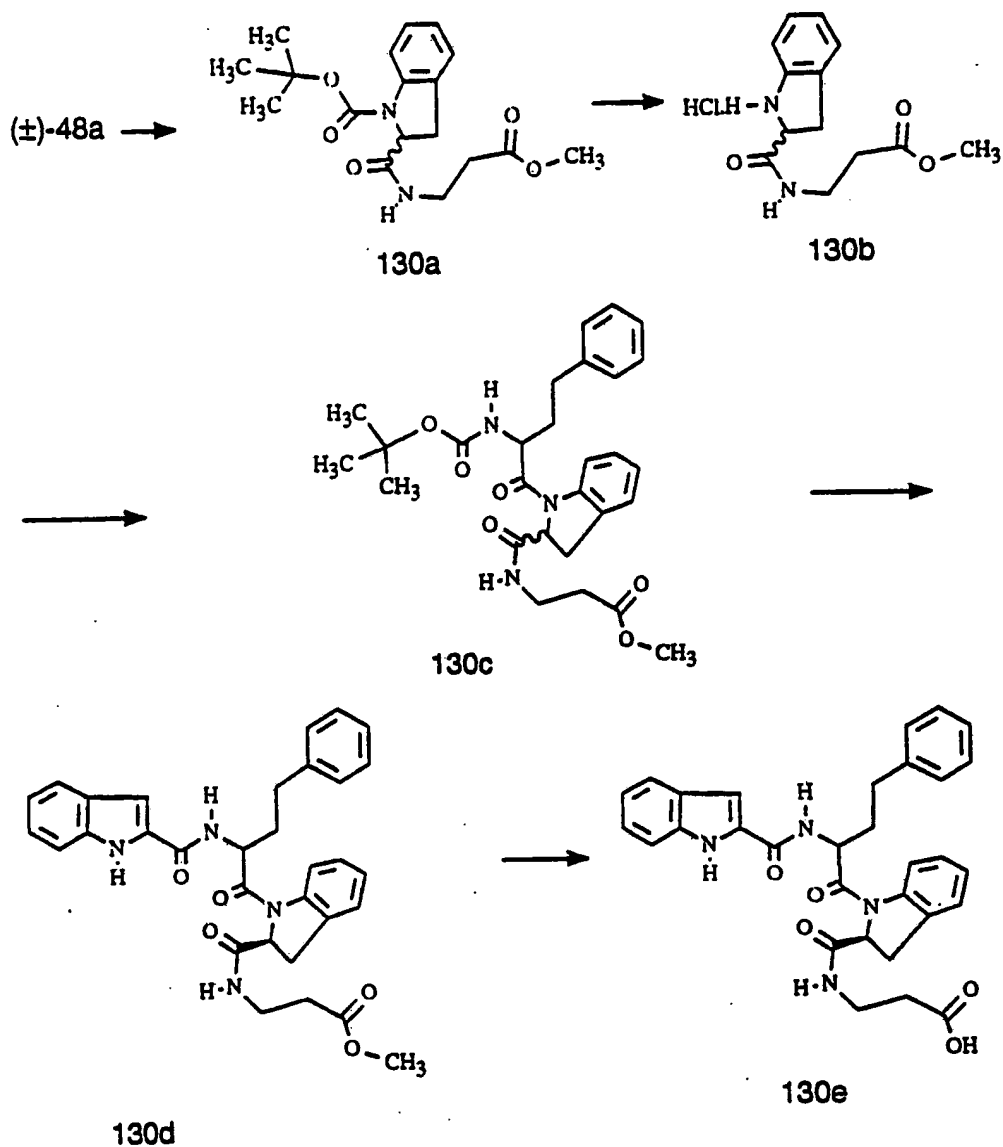
**129d** N-{(2S)-1-[(2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl]-2,3-dihydroindole-2-acetyl}-glycine.

This was prepared from 129c on a 0.16 mmol scale following the method described for 1f. The product was isolated in 30% yield (26 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 90:10:2 v/v/v).

HPLC System A  $t_R$ =13.6' >95%

Mass spec (FAB)  $m/e$ =539 [M+H]<sup>+</sup>

## EXAMPLE 130



**130a** Methyl 3-((2RS)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-propanoate.

This was prepared from racemic 48a and  $\beta$ -alanineOMe on a 1.8 mmol scale following the method described for 1d. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

**130b Methyl 3-((2RS)-2,3-dihydroindole-2-carboxylamino)-propanoic acid hydrochloride.**

This was prepared from 130a on a 1.2 mmol scale following the method described for 1c. The product was used without purification, assuming a yield of 100%.

**130c Methyl 3-((2RS)-1-((2S)-2-(*tert*-butoxycarbonylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-carboxylamino)-propanoic acid.**

This was prepared from 130b and BOC-homophenylalanine on a 1.2 mmol scale following the method described for 1d. The product was isolated in 41% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 45:55 v/v).

**130d Methyl 3-((2S)-1-((2S)-2-(indole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-carboxylamino)-propanoic acid.**

This was prepared from 130c on a 0.49 mmol scale following the method described for 123b. The product was isolated in 28% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 55:45 v/v).

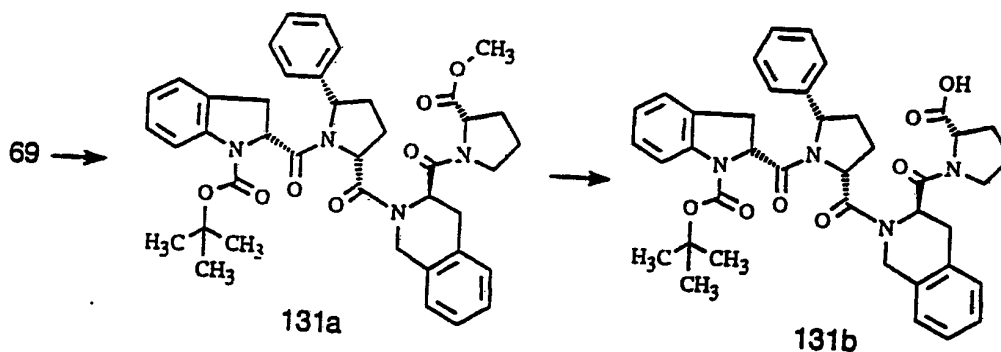
**130e 3-((2S)-1-((2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-carboxylamino)-propanoic acid.**

This was prepared from 130d on a 0.09 mmol scale following the method described for 1f. The product was isolated in 97% yield (47 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:2 v/v/v).

HPLC System A  $t_R$ =12.6' >95%

Mass spec (FAB)  $m/e$ =539  $[M+H]^+$

## EXAMPLE 131





**131a Methyl N-((3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-prolinate.**

This was prepared from 69 and ProOMe on a 0.30 mmol scale following the method described for 1d. The product was isolated in 18% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 then 70:30 v/v).

R<sub>f</sub> (EtOAc:hexane 70:30 v/v) 0.22

**131b N-((3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-proline.**

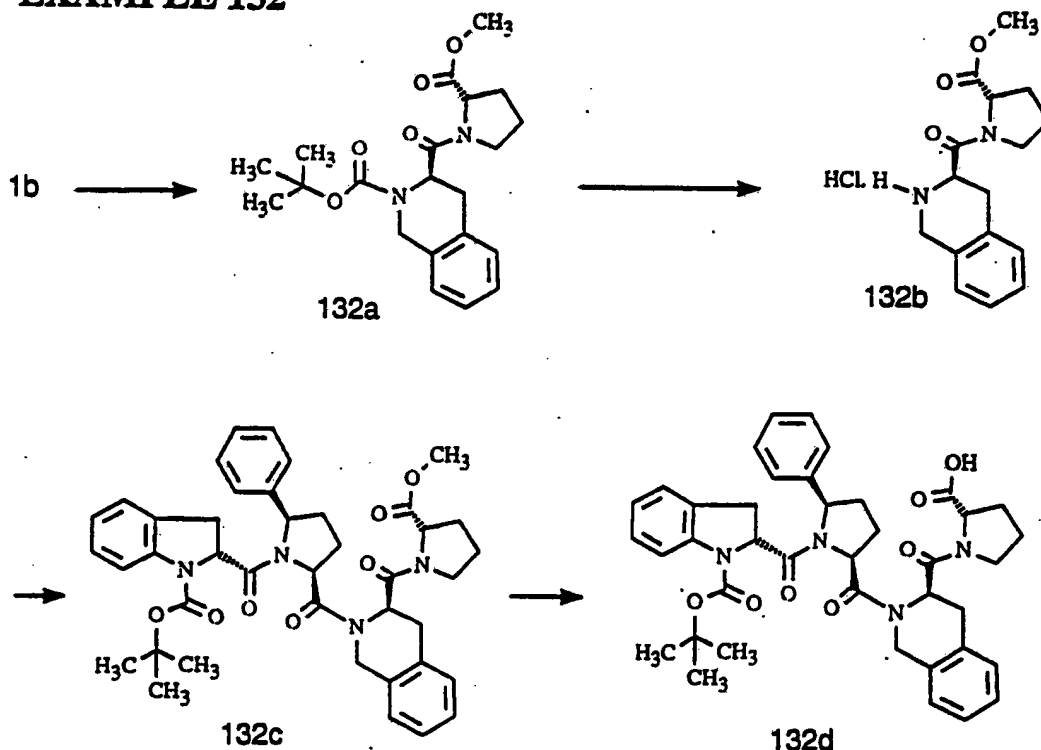
This was prepared from 131a on a 0.06 mmol scale following the method described for 1f. The product was isolated in 49% yield (19 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A t<sub>R</sub>=19.7' >98%

AAA Peptide content=73%

Mass spec (FAB) m/e=693 [M+H]<sup>+</sup>

### EXAMPLE 132



**132a Methyl N-((3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-prolinate.**

This was prepared from 1a and ProOMe on a 5.4 mmol scale following the method described for 1d. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:hexane 70:30 v/v).

**132b Methyl N-((3R)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-prolinate hydrochloride.**

This was prepared from 132a on a 0.13 mmol scale following the method described for 1c. The product was used without purification assuming a yield of 100%.

**132c Methyl N-((3R)-2-((2S,5R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-prolinate.**

This was prepared from 132b and 88b on a 0.13 mmol scale following the method described for 1d. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 65:35 v/v).

R<sub>f</sub> (EtOAc:hexane 80:20 v/v) 0.38

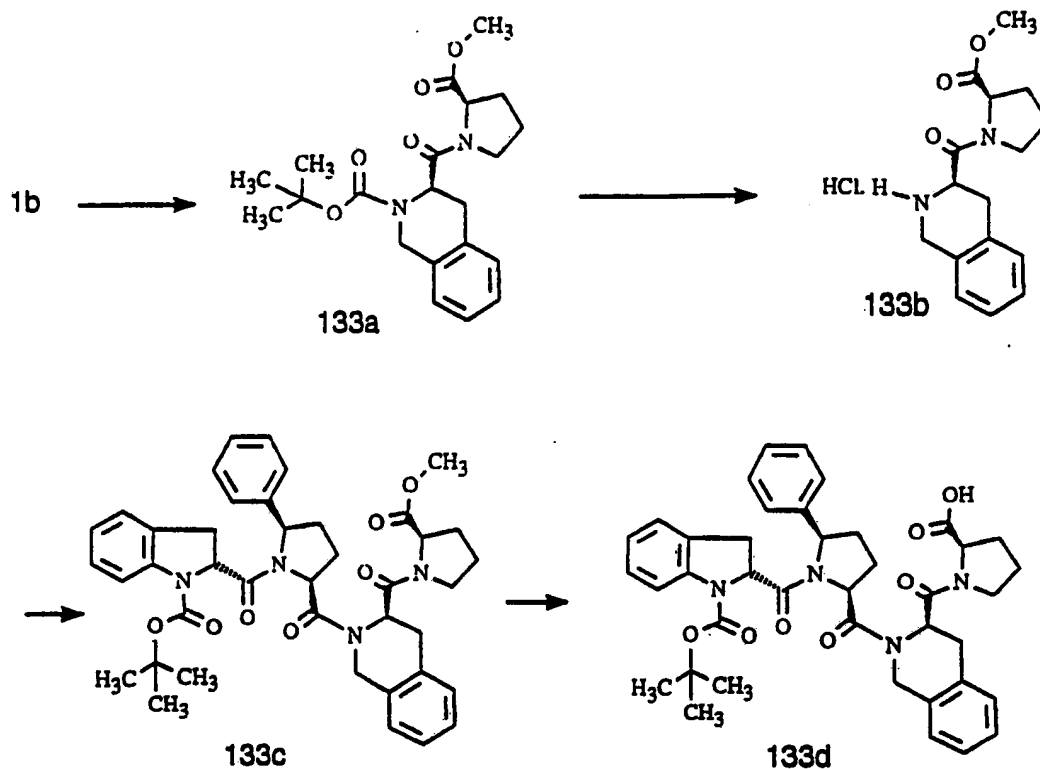
**132d N-((3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-proline.**

This was prepared from 132c on a 0.13 mmol scale following the method described for 1f. The product was isolated in 24% yield (21 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 90:10:2 v/v/v).

HPLC System A t<sub>R</sub>=19.9' >95%

AAA Peptide content=81%

Mass spec (FAB) m/e=693 [M+H]<sup>+</sup>

**EXAMPLE 133**

**133a** Methyl N-[(3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carbonyl]-D-prolinate.

This was prepared from 1a and D-ProOMe on a 0.56 mmol scale following the method described for 1d. The product was isolated in 39% yield after flash chromatography on silica gel (eluant EtOAc:hexane 65:35 v/v).

$R_f$  (EtOAc:hexane 70:30 v/v) 0.30

**133b** Methyl N-[(3R)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl]-D-prolinate hydrochloride.

This was prepared from 133a on a 0.13 mmol scale following the method described for 1c. The product was used without purification assuming a yield of 100%.

**133c** Methyl N-((3R)-2-((2S,5R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-D-prolinate.

This was prepared from 133b and 88b on a 0.13 mmol scale following the method described for 1d. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 65:35 v/v).

R<sub>f</sub> (EtOAc:hexane 80:20 v/v) 0.30

**133d** N-((3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-D-proline.

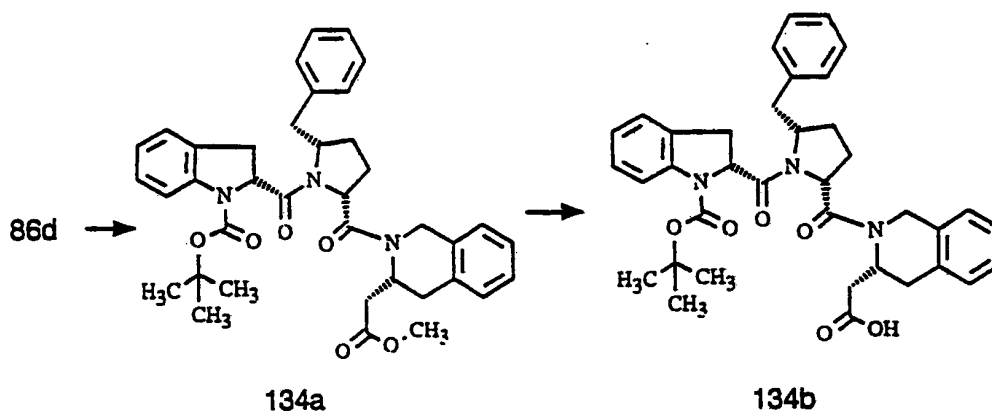
This was prepared from 133c on a 0.13 mmol scale following the method described for 1f. The product was isolated in 57% yield (51 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 95:5:2 v/v/v).

HPLC System A t<sub>R</sub>=20.2' >95%

AAA Peptide content=91%

Mass spec (FAB) m/e=693 [M+H]<sup>+</sup>

## EXAMPLE 134



**134a Methyl (3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

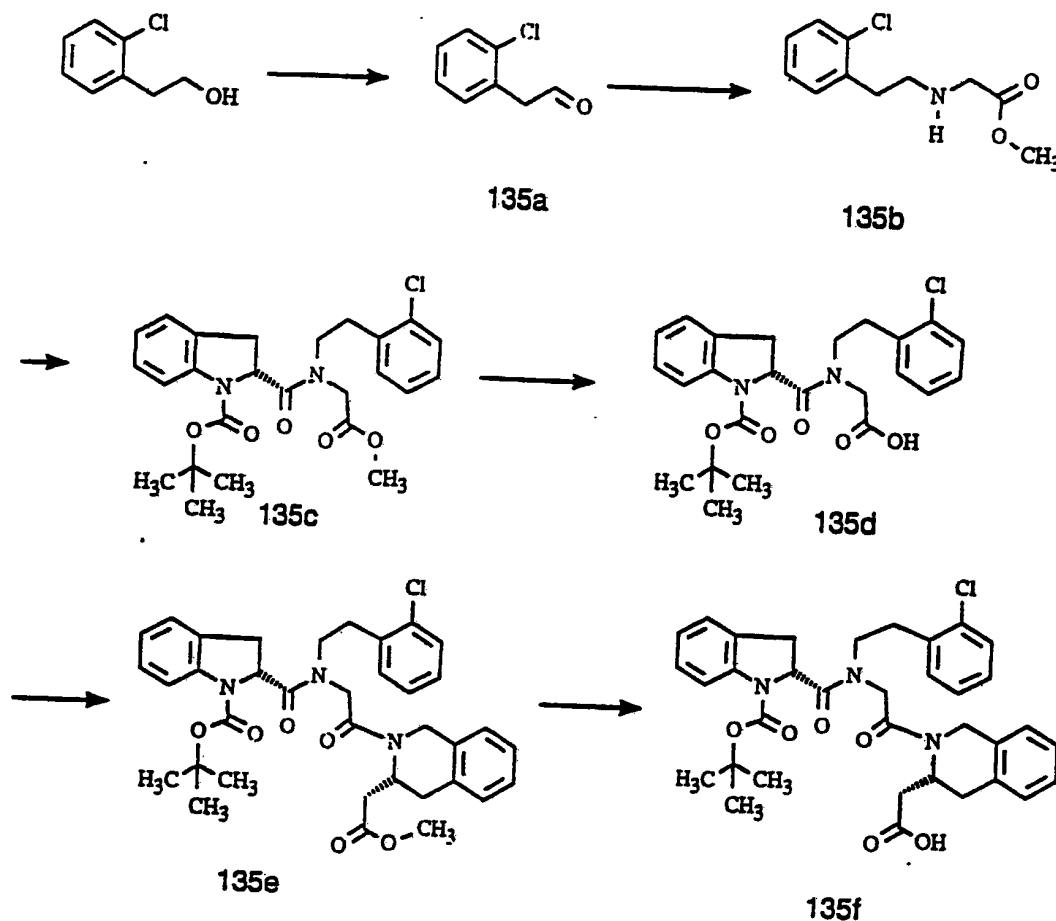
This was prepared from 26a and 86d on a 0.5 mmol scale following the method described for 1d. The product was isolated in 96% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

**134b (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 134a on a 0.48 mmol scale following the method described for 1f. The product was isolated in 51% yield (151 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:2 v/v/v).

HPLC System A  $t_R$ =14.4' >99%

Mass spec (FAB)  $m/e$ =510 [M+H-BOC]<sup>+</sup>

**EXAMPLE 135****135a 2-Chlorophenylacetaldehyde.**

This was prepared from 2-chlorophenethyl alcohol on a 9.58 mmol scale following the method described for 99a. The product was used without purification assuming a yield of 100%.

**135b Methyl N-2-chlorophenethyl-glycinate.**

This was prepared from 135a on a 9.58 mmol scale following the method described for 42a. The product was isolated in 8% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

$R_f$  (EtOAc:hexane 80:20 v/v) 0.12

$^1\text{H NMR}$   $\delta$  2.84-2.88 (4H,m); 3.40 (2H,s); 3.66 (3H,s); 7.06-7.29 (4H,m)

**135c** Methyl N-2-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from 135b and 48a on a 0.68 mmol scale following the method described for 1d. The product was isolated in 76% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R<sub>f</sub> (EtOAc:hexane 40:60 v/v) 0.26

**135d** N-2-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from 135c on a 0.52 mmol scale following the method described for 1f. The product was isolated in 78% yield and used without further purification.

**135e** Methyl (3R)-2-{N-2-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 135d and 1c on a 0.20 mmol scale following the method described for 1d. The product was isolated in 58% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

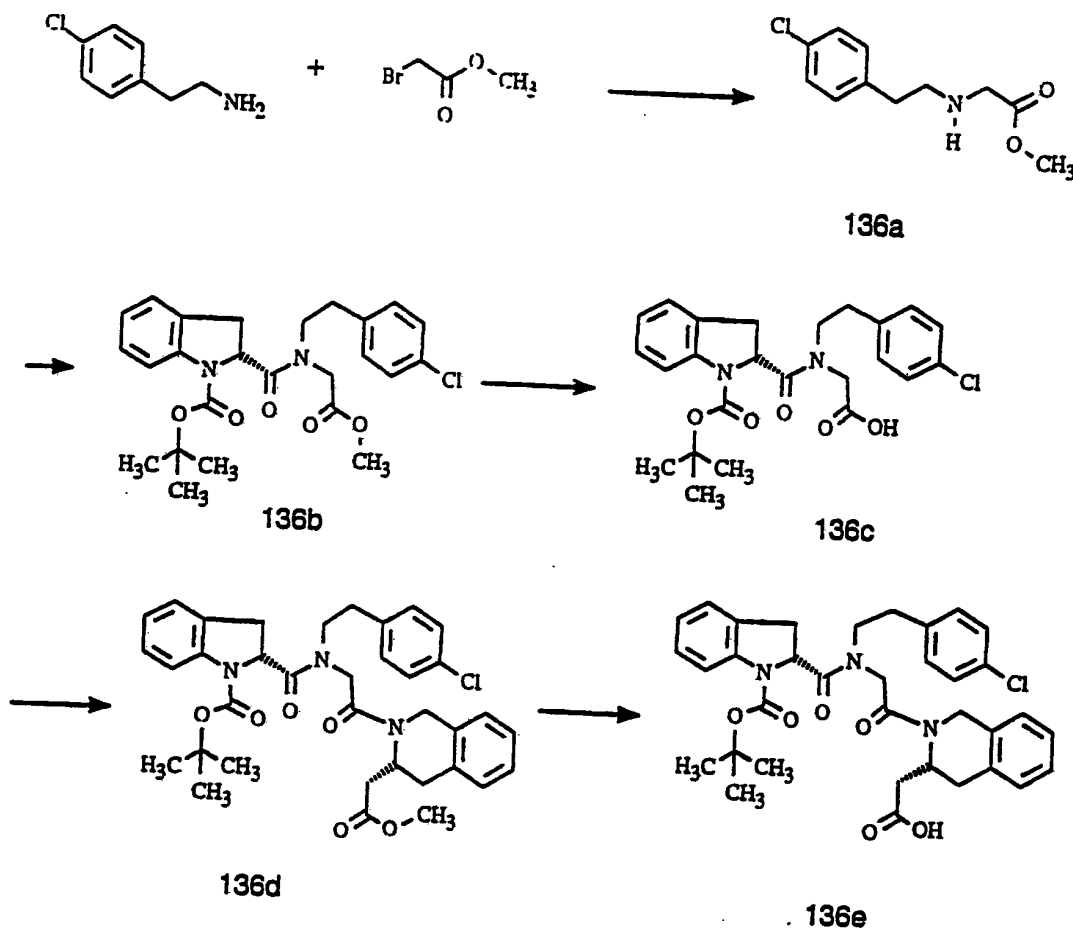
R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.25

**135f** (3R)-2-{N-2-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 135e on a 0.12 mmol scale following the method described for 1f. The product was isolated in 50% yield (38 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

HPLC System A t<sub>R</sub>=22.3' >90%

Mass spec (FAB) m/e=632 [M+H]<sup>+</sup>

**EXAMPLE 136****136a Methyl N-4-chlorophenethyl-glycinate.**

This was prepared from 2-chlorophenethylamine on a 6.43 mmol scale following the method described for 32a. The product was isolated in 94% yield and used without purification.

**136b Methyl N-4-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 136a and 48a on a 1.7 mmol scale following the method described for 1d. The product was isolated in 84% yield after flash chromatography on silica gel (eluant EtOAc:hexane 45:55 v/v).

$R_f$  (EtOAc:hexane 50:50 v/v) 0.30



**136c** N-4-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from 136b on a 1.48 mmol scale following the method described for 1f. The product was isolated in 75% yield and used without further purification.

**136d** Methyl (3R)-4-{N-2-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 136c and 1c on a 0.56 mmol scale following the method described for 1d. The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:hexane 45:55 v/v).

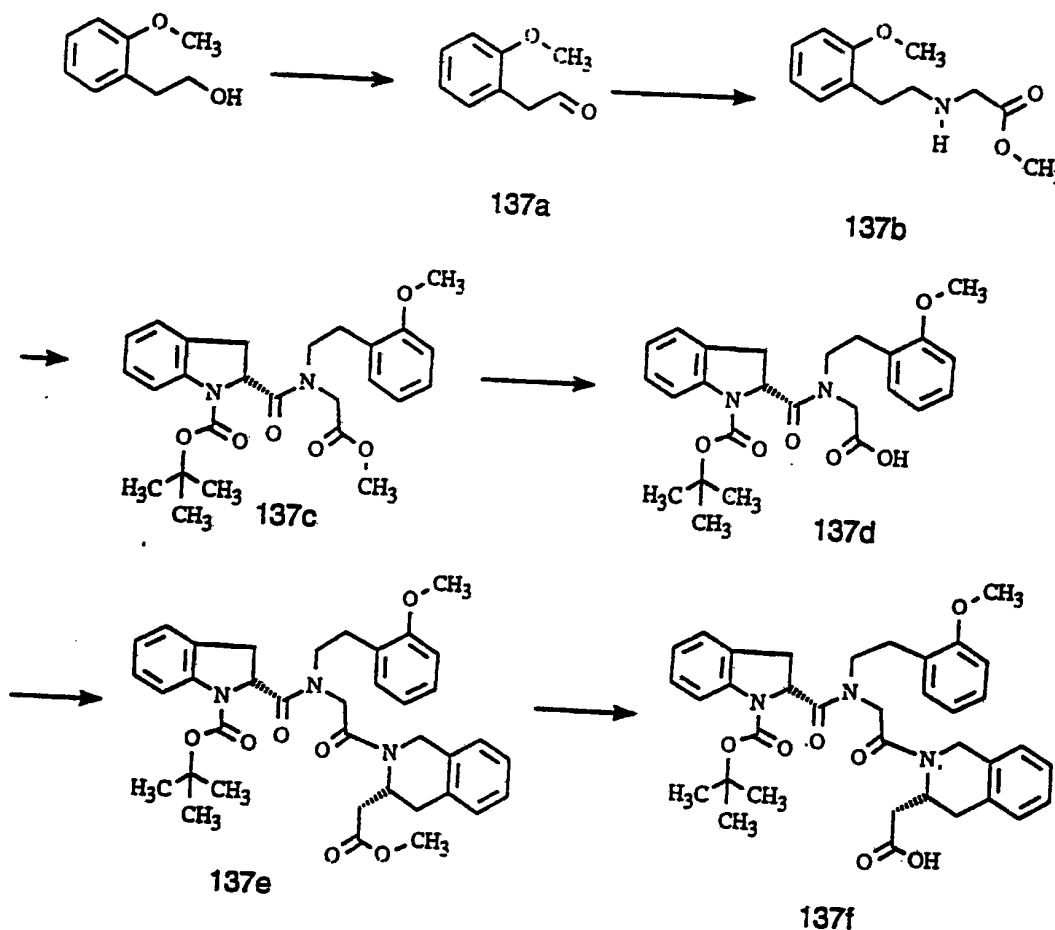
R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.26

**136e** (3R)-2-{N-4-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 136d on a 0.39 mmol scale following the method described for 1f. The product was isolated in 60% yield (149 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:hexane:AcOH 65:35:2 v/v/v).

HPLC System A t<sub>R</sub>=16.3' >95%

Mass spec (FAB) m/e=628 [M+H]<sup>+</sup>

**EXAMPLE 137****137a 2-Methoxyphenylacetaldehyde.**

This was prepared from 2-methoxyphenethyl alcohol on a 13.1 mmol scale following the method described for 99a. The product was isolated in 51% yield after flash chromatography on silica gel (eluant EtOAc:hexane 4:96 then 5:95 v/v).

$R_f$  (EtOAc:hexane 5:95 v/v) 0.17

$^1\text{H NMR}$   $\delta$  3.57 (2H,d,J=2Hz); 3.75 (3H,s); 6.8-7.3 (4H,m); 9.61 (1H,t,J=2Hz)

**137b Methyl N-2-methoxyphenethyl-glycinate.**

This was prepared from 137a on a 6.8 mmol scale following the method described for 42a. The product was isolated in 28% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

$R_f$  (EtOAc:hexane 80:20 v/v) 0.16

**137c Methyl N-2-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 137b and 48a on a 1.9 mmol scale following the method described for 1d. The product was isolated in 98% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.33

**137d N-2-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 137c on a 1.90 mmol scale following the method described for 1f. The product was isolated in 85% yield and used without further purification.

**137e Methyl (3R)-2-{N-2-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 137d and 1c on a 0.81 mmol scale following the method described for 1d. The product was isolated in 92% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

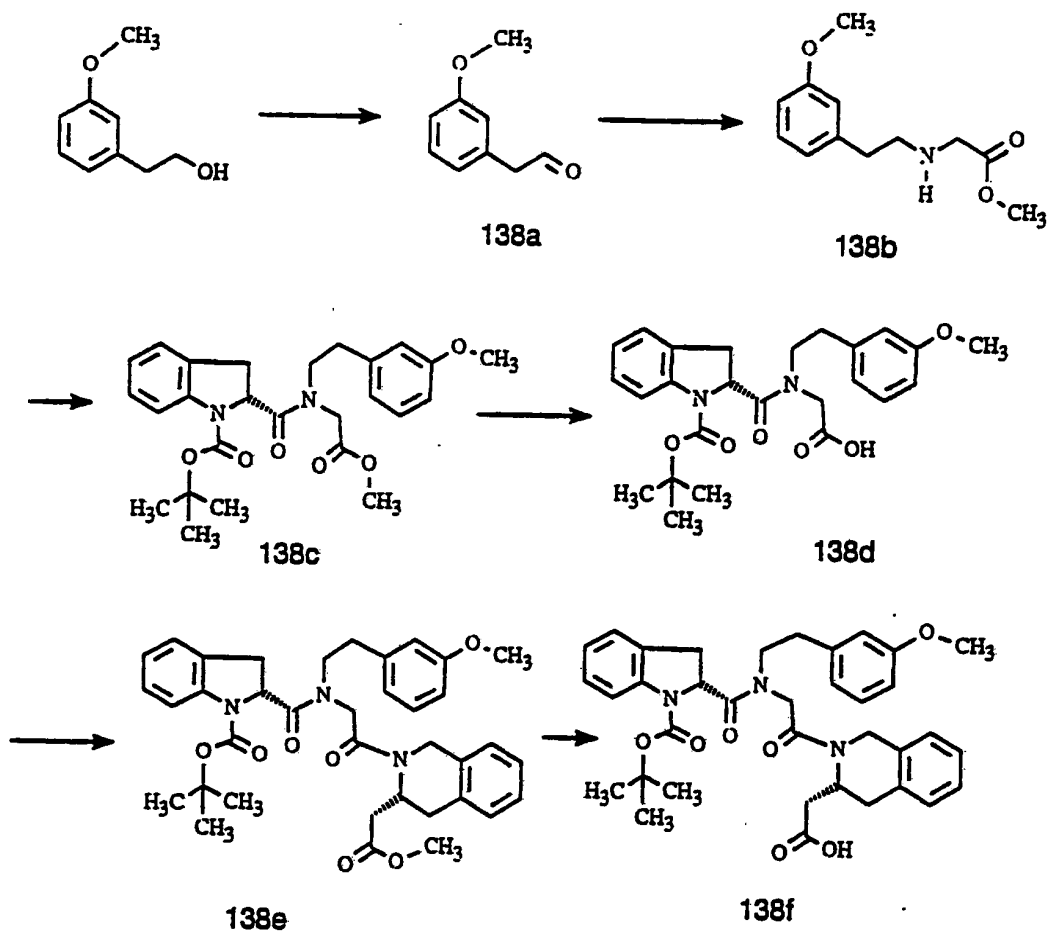
R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.28

**137f (3R)-2-{N-2-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 137e on a 0.75 mmol scale following the method described for 1f. The product was isolated in 52% yield (247 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v).

HPLC System A t<sub>R</sub>=21.1' >95%

Mass spec (FAB) m/e=628 [M+H]<sup>+</sup>

**EXAMPLE 138****138a 3-Methoxyphenylacetaldehyde.**

This was prepared from 3-methoxyphenethyl alcohol on a 13.1 mmol scale following the method described for 99a. The product was isolated in 19% yield after flash chromatography on silica gel (eluant EtOAc:hexane 10:90 v/v).

$R_f$  (EtOAc:hexane 10:90 v/v) 0.20

$^1H$  NMR  $\delta$  3.58 (2H,d,J=2.5Hz); 3.73 (3H,s); 6.6-7.2 (4H,m); 9.67 (1H,t,J=2.5Hz)

**138b Methyl N-3-methoxyphenethyl-glycinate.**

This was prepared from 138a on a 2.6 mmol scale following the method described for 42a. The product was isolated in 42% yield after flash chromatography on silica gel (eluant EtOAc:hexane 90:10 v/v).

$R_f$  (EtOAc:hexane 90:10 v/v) 0.16

**138c Methyl N-3-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 138b and 48a on a 1.1 mmol scale following the method described for 1d. The product was isolated in 86% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R<sub>f</sub> (EtOAc:hexane 40:60 v/v) 0.30

**138d N-3-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 138c on a 0.93 mmol scale following the method described for 1f. The product was used without further purification assuming a 100% yield.

**138e Methyl (3R)-2-{N-3-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 138d and 1c on a 0.47 mmol scale following the method described for 1d. The product was isolated in 91% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

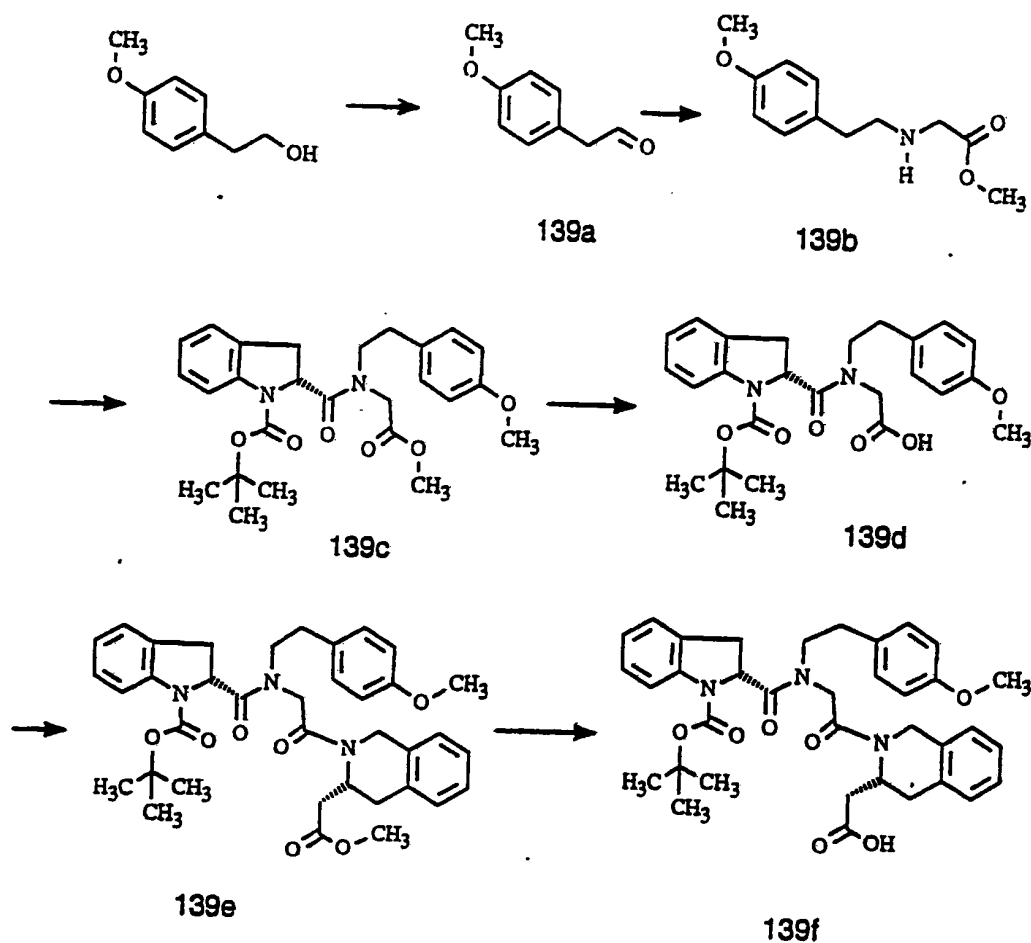
R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.23

**138f (3R)-2-{N-3-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 138e on a 0.43 mmol scale following the method described for 1f. The product was isolated in 11% yield (31 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

HPLC System A t<sub>R</sub>=19.6' >80%

Mass spec (FAB) m/e=628 [M+H]<sup>+</sup>

**EXAMPLE 139****139a 4-Methoxyphenylacetaldehyde.**

This was prepared from 4-methoxyphenethyl alcohol on a 13.1 mmol scale following the method described for 99a. The product was isolated in 17% yield after flash chromatography on silica gel (eluant EtOAc:hexane 10:90 v/v).

$R_f$  (EtOAc:hexane 10:90 v/v) 0.20

$^1H$  NMR  $\delta$  3.75 (2H,d,J=2.3Hz); 3.75 (3H,s); 7.03 (2H,d,J=9Hz); 7.25 (2H,d,J=9Hz); 9.84 (1H,t,J=2.3Hz)

**139b Methyl N-4-methoxyphenethyl-glycinate.**

This was prepared from 139a on a 2.3 mmol scale following the method described for 42a. The product was isolated in 38% yield after flash chromatography on silica gel (eluant EtOAc:hexane 90:10 v/v).

$R_f$  (EtOAc:hexane 90:10 v/v) 0.17

**139c Methyl N-4-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 139b and 48a on a 0.87 mmol scale following the method described for 1d. The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.30

**139d N-4-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 139c on a 0.72 mmol scale following the method described for 1f. The product was isolated in 80% yield and used without further purification.

**139e Methyl (3R)-2-{N-4-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 139d and 1c on a 0.29 mmol scale following the method described for 1d. The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

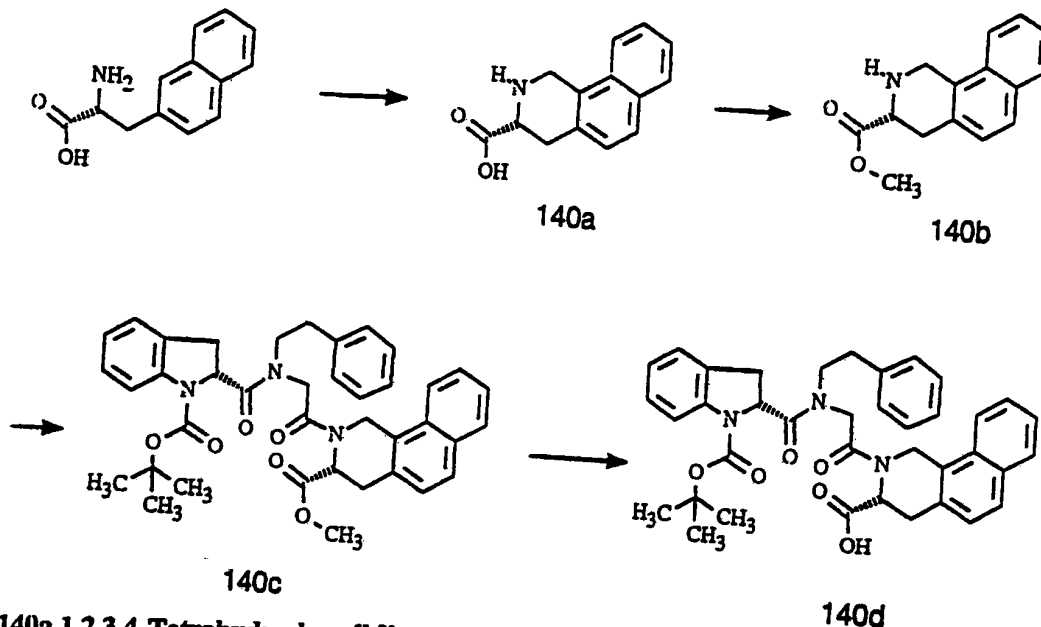
R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.21

**139f (3R)-2-{N-4-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 139e on a 0.22 mmol scale following the method described for 1f. The product was isolated in 47% yield (65 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

HPLC System A t<sub>R</sub>=19.6' >80%

Mass spec (FAB) m/e=628 [M+H]<sup>+</sup>

**EXAMPLE 140****140a 1,2,3,4-Tetrahydro-benz[h]isoquinoline-3-carboxylic acid.**

This was prepared from  $\beta$ -(2-naphthyl)alanine on a 23 mmol scale following the method described for 84a. The product was isolated in 85% yield as a mixture of benz[g]- and benz[h]-fused isomers which was used without further purification.

**140b Methyl 1,2,3,4-tetrahydro-benz[h]isoquinoline-3-carboxylate.**

This was prepared from 140a on a 9.9 mmol scale following the method described for 26a. The product was isolated in 2% yield after flash chromatography on silica gel (eluant EtOAc). The benz[g]-fused isomer was also isolated (in 4% yield).

**140c Methyl (3R)-2-{N-phenethyl-N-((2R)-1-tert-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[h]isoquinoline-3-carboxylate.**

This was prepared from 90b and 140b on a 0.19 mmol scale following the method described for 1d. The product was isolated in 33% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**140d (3R)-2-{N-Phenethyl-N-((2R)-1-tert-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[h]isoquinoline-3-carboxylic acid.**

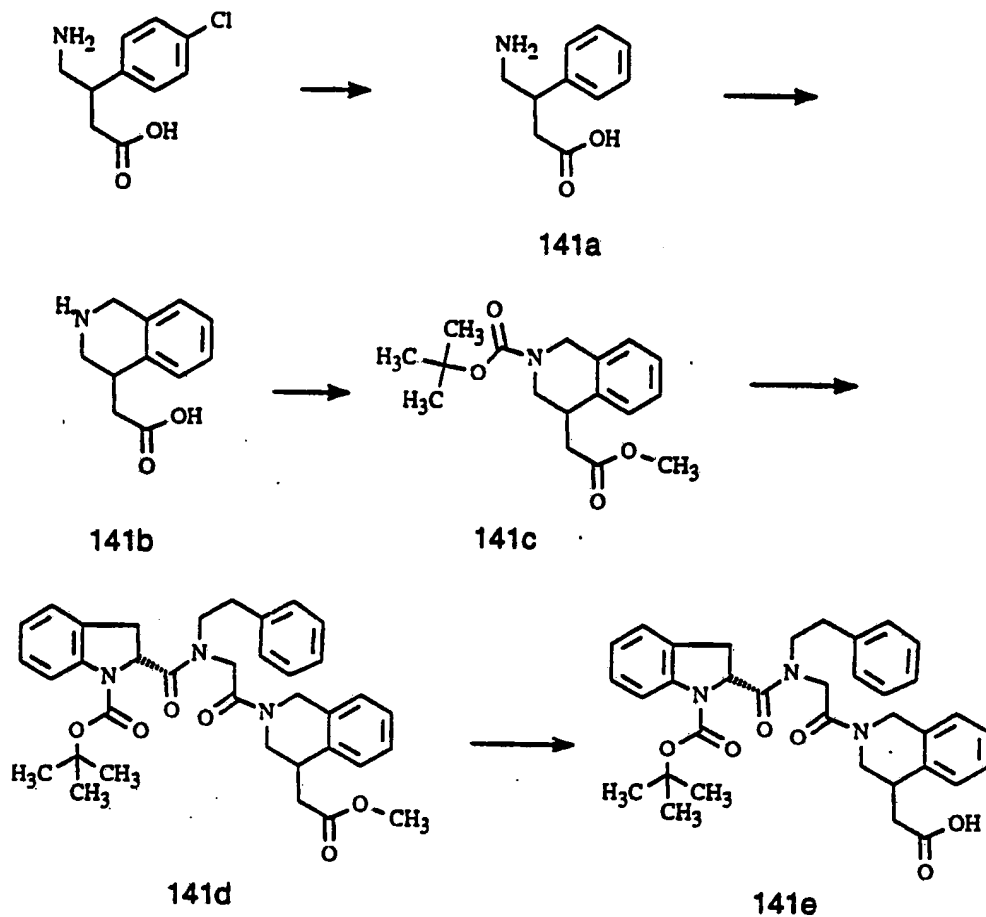
This was prepared from 140c on a 0.06 mmol scale following the method described for 1f. The product was isolated in 47% yield (18 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:2 v/v/v).



HPLC System A  $t_R=21.9'$  >80%

Mass spec (FAB)  $m/e=407$

### EXAMPLE 141



#### 141a (3RS)-4-Amino-3-phenylbutanoic acid.

A suspension of (RS)-4-amino-3-(4-chlorophenyl)butanoic acid in  $H_2O$  (100 mL) and MeOH (70 mL) was hydrogenated over 5% Pd-on-carbon at room temperature for 5 hr. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo* to give the title compound which was used without further purification assuming a yield of 100%.

#### 141b (4RS)-1,2,3,4-Tetrahydroisoquinoline-4-acetic acid.

This was prepared from 141a on a 4.7 mmol scale following the method described for 84a. The product was used without further purification assuming a yield of 100%.

**141c Methyl (4RS)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-4-acetate.**

This was prepared from 141b on a 4.7 mmol scale in two steps. The acid was esterified following the method described for 26a. The crude product was taken up in  $\text{CH}_2\text{Cl}_2$  (70 mL) and treated with  $\text{BOC}_2\text{O}$  (1.31 g, 6 mmol) and *i*- $\text{Pr}_2\text{NEt}$  (excess). The mixture was stirred at room temperature overnight, diluted with EtOAc, washed with aq.  $\text{KHSO}_4$  and brine, filtered (Whatman IPS phase separator), and concentrated *in vacuo*. The product was isolated in 25% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

**141d Methyl (4RS)-2-{N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-4-acetate.**

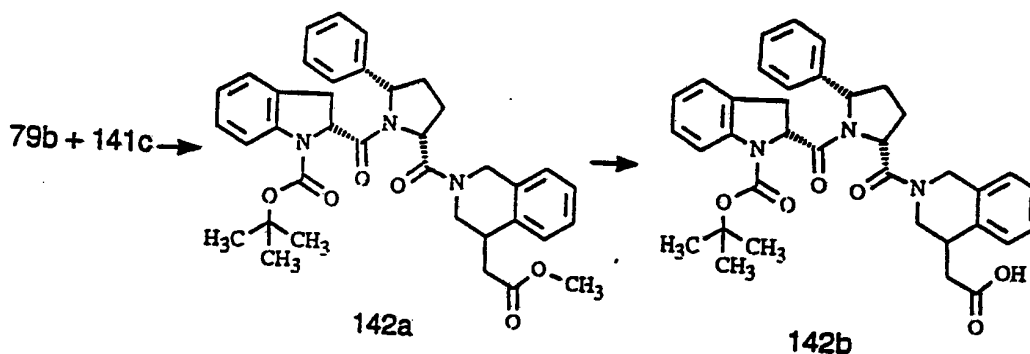
This was prepared from 90b and 141c on a 0.50 mmol scale following the method described for 79d. The product was isolated in 39% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

**141e (4RS)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-4-acetic acid.**

This was prepared from 141d on a 0.19 mmol scale following the method described for 1f. The product was isolated in 70% yield (79 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System A  $t_R=19.0'$  >90%

Mass spec (FAB)  $m/e=598$   $[\text{M}+\text{H}]^+$

**EXAMPLE 142**

**142a** Methyl (4RS)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-4-acetate.

This was prepared from 79b and 141c on a 0.52 mmol scale following the method described for 79d. The product was isolated in 48% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

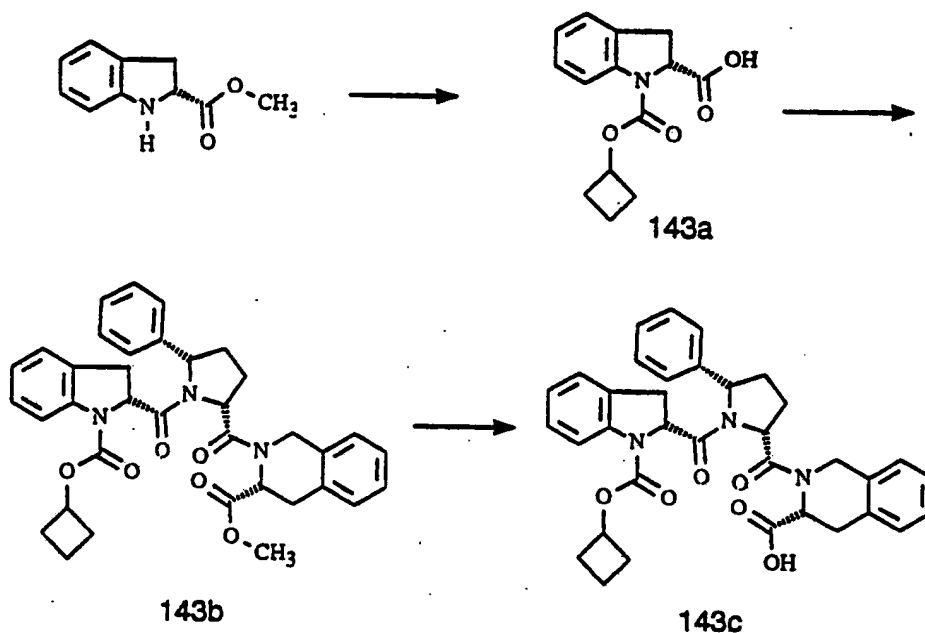
**142b** (4RS)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-4-acetic acid.

This was prepared from 142a on a 0.16 mmol scale following the method described for 1f. The product was isolated in 71% yield (69 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System A  $t_R=20.2'$  >95%

Mass spec (FAB)  $m/e=610$   $[M+H]^+$

### EXAMPLE 143



**143a** (2R)-1-Cyclobutyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from cyclobutanol on a 2.0 mmol scale following the method described for 72a. The product was isolated in 16% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

**143b Methyl (3R)-2-((2R,5S)-1-((2R)-1-cyclobutyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 68a and 143a on a 0.24 mmol scale following the method described for 79d. The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

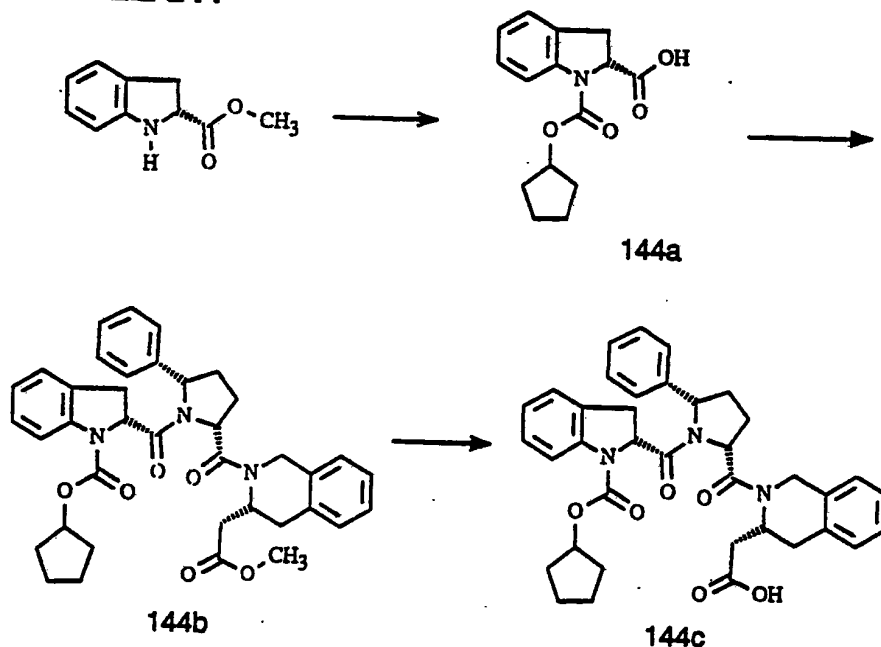
**143c (3R)-2-((2R,5S)-1-((2R)-1-Cyclobutyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 143b on a 0.20 mmol scale following the method described for 1f. The product was isolated in 72% yield (85 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 65:35:2 v/v/v).

HPLC System B  $t_R$ =14.2' >95%

Mass spec (FAB)  $m/e$ =594  $[M+H]^+$

#### EXAMPLE 144



**144a (2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from cyclopentanol on a 2.0 mmol scale following the method described for 72a. The product was isolated in 75% yield and used without purification.

**144b Methyl (3R)-2-((2R,5S)-1-((2R)-1-cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 78a and 144a on a 0.30 mmol scale following the method described for 79d. The product was isolated in 73% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

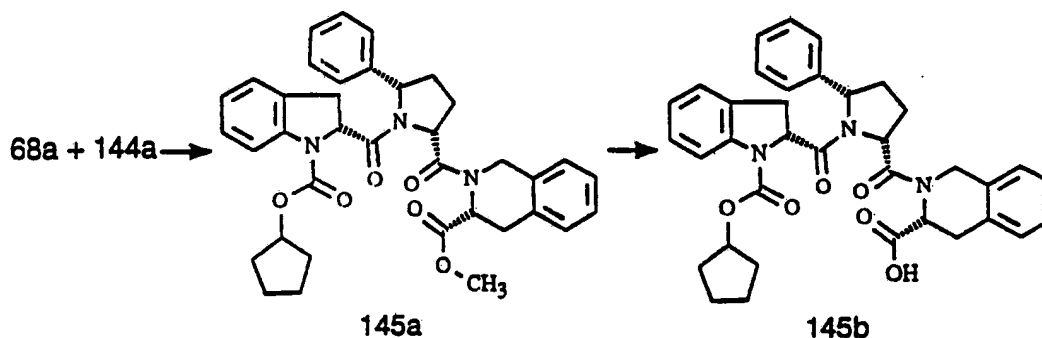
**144c (3R)-2-((2R,5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 144b on a 0.22 mmol scale following the method described for 1f. The product was isolated in 79% yield (108 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 65:35:2 v/v/v).

HPLC System B  $t_R$ =16.3' >98%

Mass spec (FAB)  $m/e$ =622  $[M+H]^+$

## EXAMPLE 145



**145a Methyl (3R)-2-((2R,5S)-1-((2R)-1-cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 68a and 144a on a 0.24 mmol scale following the method described for 79d. The product was isolated in 81% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

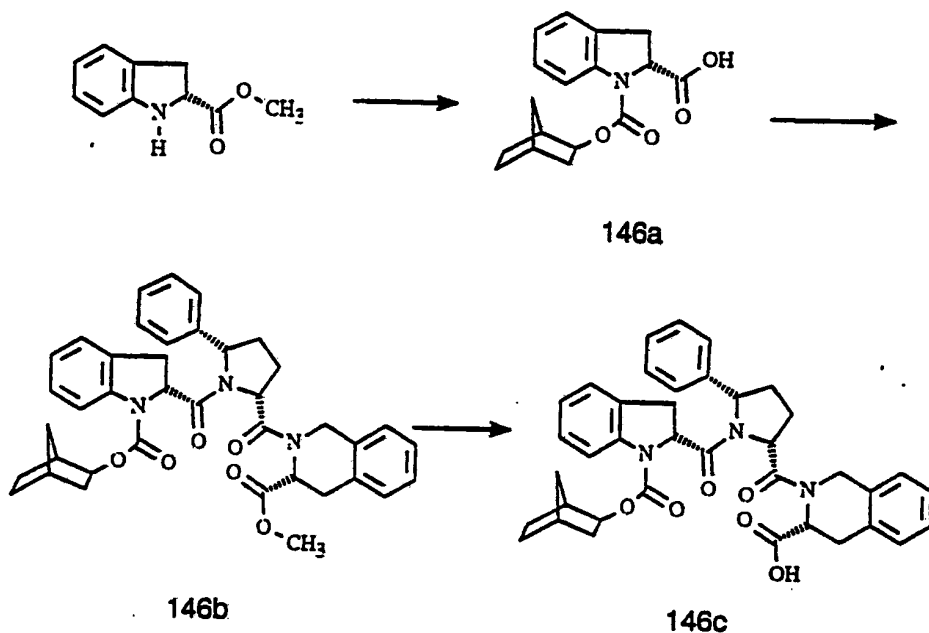
**145b** (3R)-2-((2R,5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 145a on a 0.19 mmol scale following the method described for 1f. The product was isolated in 69% yield (80 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 65:35:2 v/v/v).

HPLC System B  $t_R$ =15.2' >98%

Mass spec (FAB)  $m/e$ =608  $[M+H]^+$

## EXAMPLE 146



**146a** (2R)-1-(2-*exo*-Norbornyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from 2-*exo*-norbornyl alcohol on a 1.0 mmol scale following the method described for 72a. The product was isolated in 93% yield and used without purification.

**146b** Methyl (3R)-2-((2R,5S)-1-((2R)-1-(2-*exo*-norbornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 68a and 146a on a 0.24 mmol scale following the method described for 79d. The product was isolated in 74% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

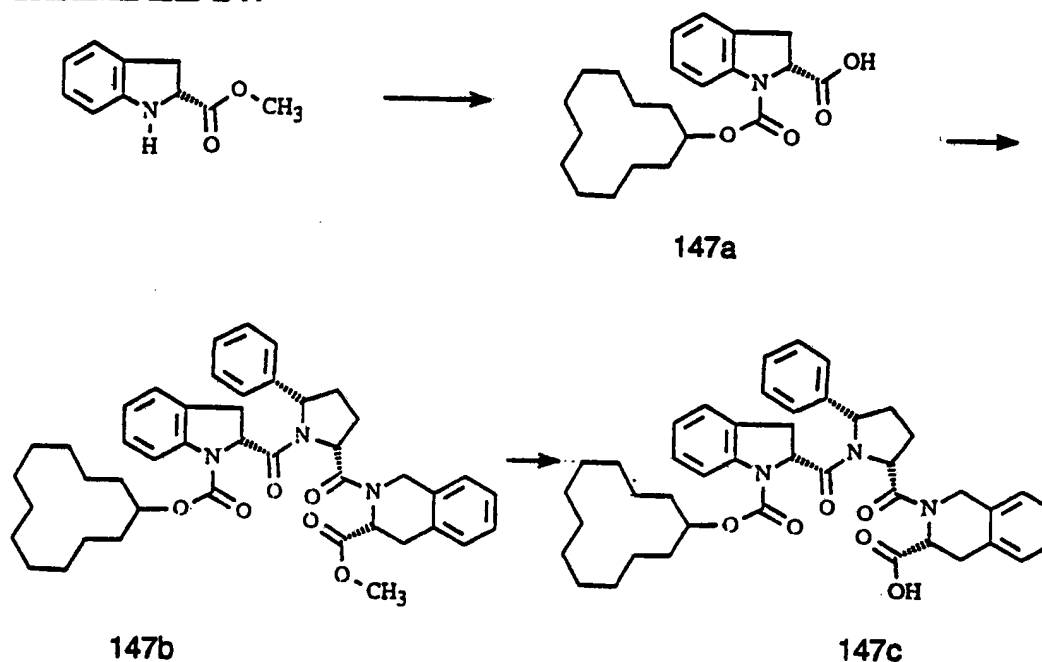
**146c (3R)-2-((2R,5S)-1-((2R)-1-(2-*exo*-Norbornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 146b on a 0.18 mmol scale following the method described for 1f. The product was isolated in 65% yield (74 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System B  $t_R$ =17.2' >98%

Mass spec (FAB)  $m/e$ =634  $[M+H]^+$

### EXAMPLE 147



**147a (2R)-1-Cyclododecyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from cyclododecanol on a 1.0 mmol scale following the method described for 72a. The product was isolated in 64% yield and used without purification.

**147b Methyl (3R)-2-((2R,5S)-1-((2R)-1-cyclododecyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 68a and 147a on a 0.24 mmol scale following the method described for 79d. The product was isolated in 55% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

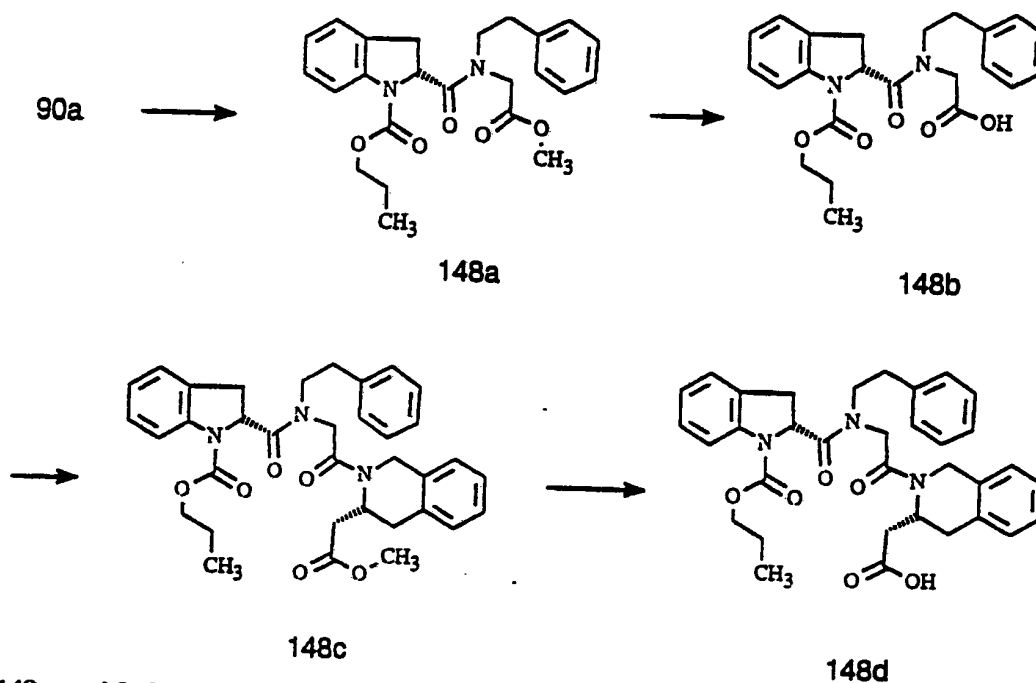
**147c** (3R)-2-[(2R,5S)-1-[(2R)-1-Cyclododecyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 147b on a 0.13 mmol scale following the method described for 1f. The product was isolated in 58% yield (53 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System B  $t_R$ =25.0' >98%

Mass spec (FAB)  $m/e$ =706  $[M+H]^+$

### EXAMPLE 148



**148a** Methyl N-phenethyl-N-[(2R)-1-*n*-propyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-glycinate.

This was prepared from 90a and propyl chloroformate on a 0.48 mmol scale following the method described for 81a. The product was isolated in 88% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).



**148b** N-Phenethyl-N-((2R)-1-*n*-propyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from 148a on a 0.42 mmol scale following the method described for 1f. The product was isolated in 45% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:2 v/v/v).

**148c** Methyl (3R)-2-{N-phenethyl-N-((2R)-1-*n*-propyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c and 148b on a 0.08 mmol scale following the method described for 1d. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v).

$R_f$  (EtOAc:hexane 60:40 v/v) 0.35

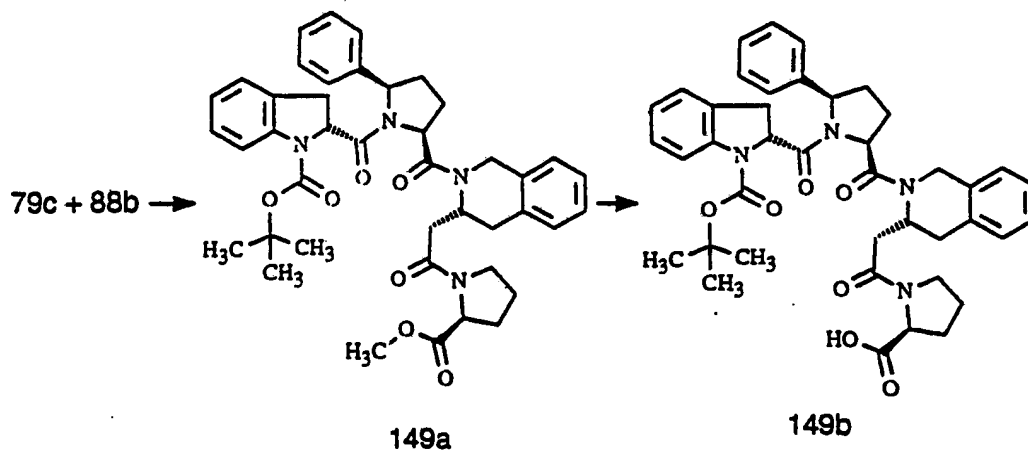
**148d** (3R)-2-{N-Phenethyl-N-((2R)-1-*n*-propyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 148c on a 0.08 mmol scale following the method described for 1f. The product was isolated in 54% yield (25 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:2 v/v/v).

HPLC System A  $t_R$ =17.9' >98%

Mass spec (FAB)  $m/e$ =584  $[M+H]^+$

## EXAMPLE 149



**149a Methyl N-((3R)-2-((2S,5R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetyl)-prolinate.**

This was prepared from 79c and 88b on a 0.14 mmol scale following the method described for 79d. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

$R_f$  (EtOAc:hexane 80:20 v/v) 0.13

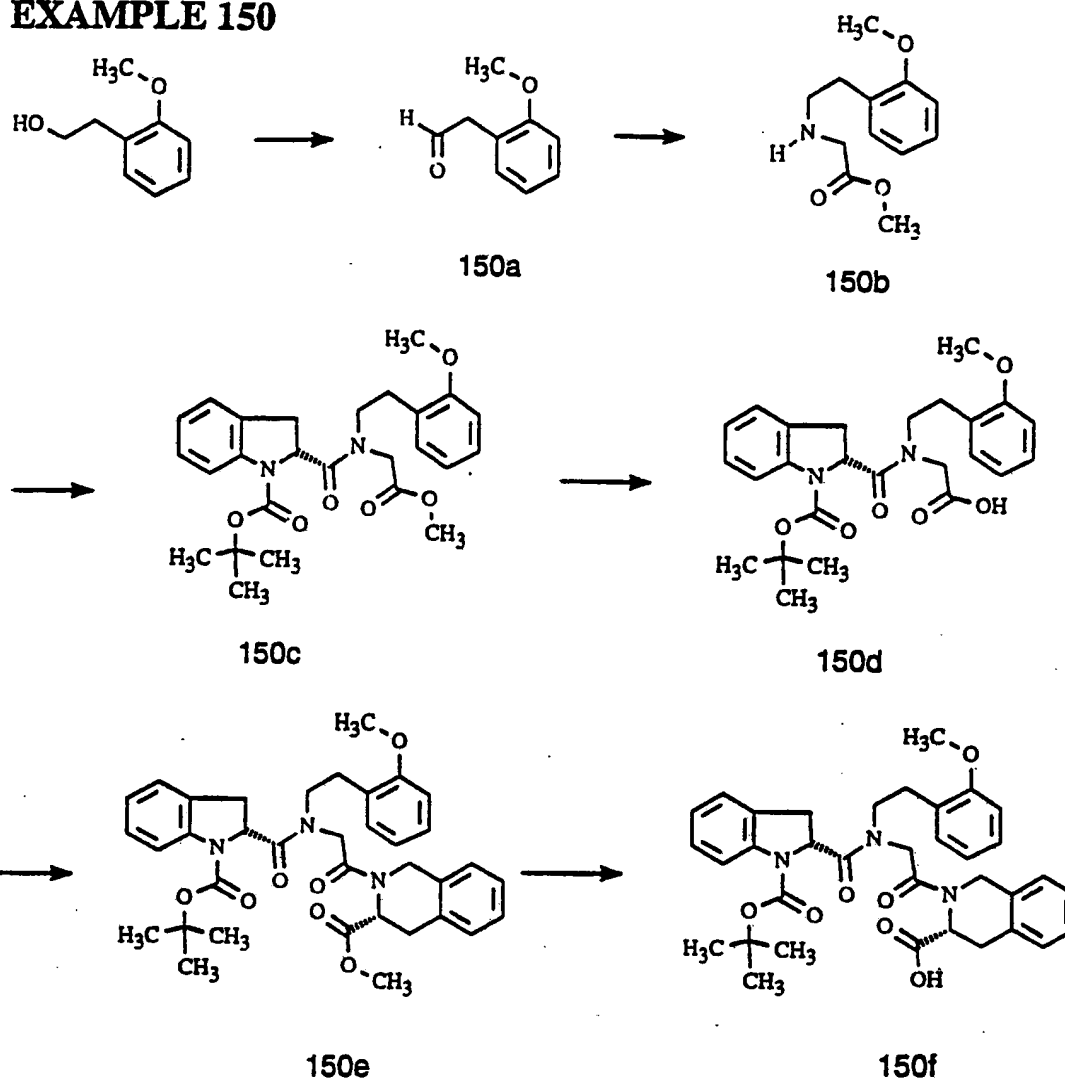
**149b N-((3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetyl)-proline.**

This was prepared from 149a on a 0.14 mmol scale following the method described for 1f. The product was isolated in 46% yield (46 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A  $t_R$ =17.6' >95%

AAA Peptide content=91%

Mass spec (FAB)  $m/e$ =707 [M+H]<sup>+</sup>

**EXAMPLE 150****150a (2-Methoxyphenyl)acetaldehyde.**

This was prepared from 2-(2-methoxyphenyl)ethanol on a 13.1 mmol scale following the method described for 99ad. The product was isolated in 52% yield after flash chromatography on silica gel (eluant EtOAc:hexane 5:95 v/v).

$R_f$  (EtOAc:hexane 5:95 v/v) 0.17

**150b Methyl N-2-(2-methoxyphenyl)ethyl-glycinate.**

This was prepared from 150a on a 6.8 mmol scale following the method described for 42a. The product was isolated in 28% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

$R_f$  (EtOAc:hexane 80:20 v/v) 0.16

**150c Methyl N-2-(2-methoxyphenyl)ethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 48a and 150b on a 1.93 mmol scale following the method described for 1d. The product was isolated in 98% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

$R_f$  (EtOAc:hexane 50:50 v/v) 0.33

**150d N-2-(2-Methoxyphenyl)ethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 150c on a 1.90 mmol scale following the method described for 1f. The product was isolated in 85% yield and used without purification.

**150e Methyl (3R)-2-{N-2-(2-methoxyphenyl)ethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 26a and 150d on a 0.81 mmol scale following the method described for 1d. The product was isolated in 94% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

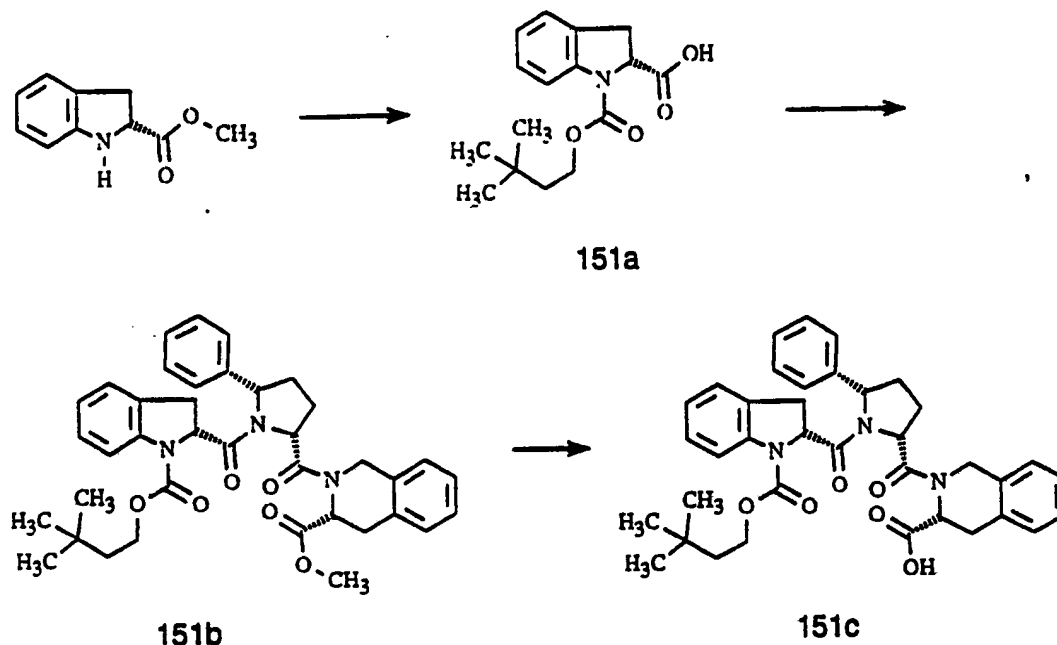
$R_f$  (EtOAc:hexane 40:60 v/v) 0.29

**150f (3R)-2-{N-2-(2-Methoxyphenyl)ethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 150e on a 0.76 mmol scale following the method described for 1f. The product was isolated in 57% yield (267 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

HPLC System A  $t_R$ =20.5' >95%

Mass spec (FAB)  $m/e$ =614  $[M+H]^+$

**EXAMPLE 151****151a (2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from 3,3-dimethylbutanol on a 2.34 mmol scale following the method described for 72a. The product was isolated in 37% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).

**151b Methyl (3R)-2-((2R,5S)-1-((2R)-1-(3,3-dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

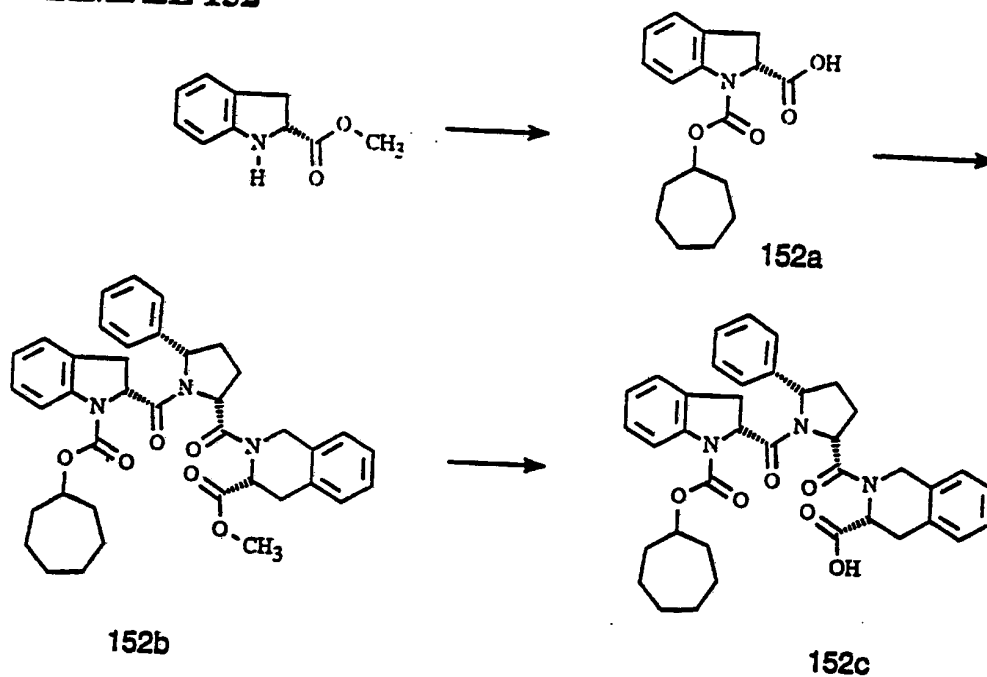
This was prepared from 68a and 151a on a 0.28 mmol scale following the method described for 79d. The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

$R_f$  (EtOAc:hexane 35:65 v/v) 0.21

**151c (3R)-2-((2R,5S)-1-((2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 151b on a 0.21 mmol scale following the method described for 1f. The product was isolated in 66% yield (87 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

HPLC System B  $t_R=17.8'$  >95%  
 Mass spec (FAB)  $m/e=624$   $[M+H]^+$

**EXAMPLE 152**

**152a 1-((2R)-1-Cycloheptyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from cycloheptanol on a 2.35 mmol scale following the method described for 72a. The product was isolated in 39% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).

**152b Methyl (3R)-2-((2R,5S)-1-((2R)-1-cycloheptyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 68a and 152a on a 0.28 mmol scale following the method described for 79d. The product was isolated in 86% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

$R_f$  (EtOAc:hexane 35:65 v/v) 0.22

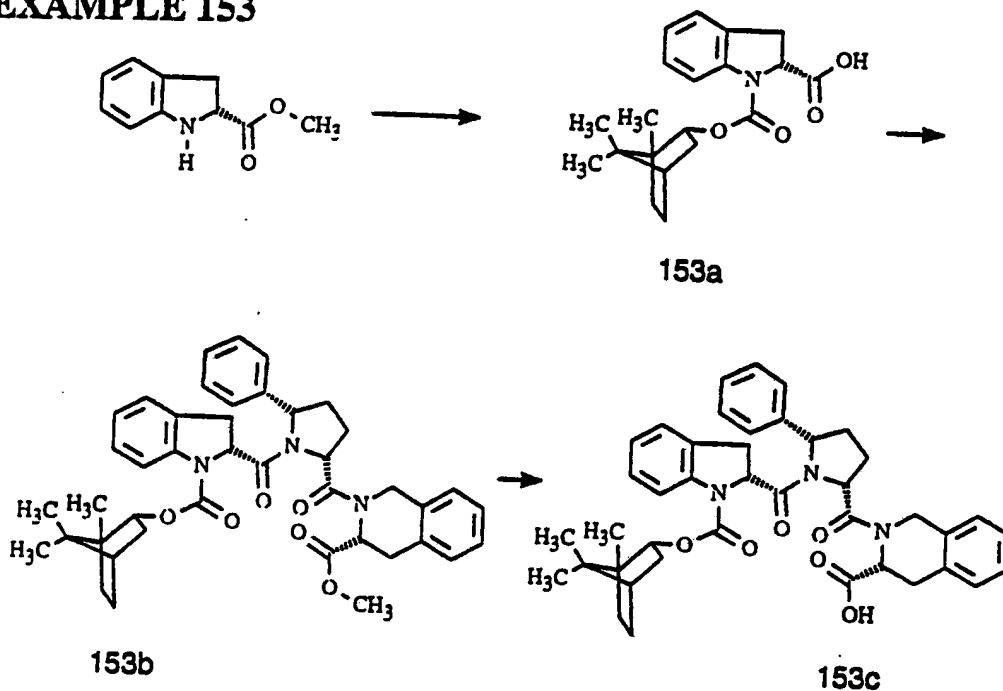
**152c** (3R)-2-((2R,5S)-1-((2R)-1-Cycloheptyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 152b on a 0.24 mmol scale following the method described for 1f. The product was isolated in 51% yield (78 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

HPLC System B  $t_R$ =18.2' >98%

Mass spec (FAB)  $m/e$ =636  $[M+H]^+$

### EXAMPLE 153



**153a** (2R)-1-((1S)-*endo*-Bornyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from (1S)-*endo*-borneol on a 2.34 mmol scale following the method described for 72a. The product was isolated in 59% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).

**153b** Methyl (3R)-2-((2R,5S)-1-((2R)-1-((1S)-*endo*-bornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 68a and 153a on a 0.28 mmol scale following the method described for 79d. The product was isolated in 66% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

$R_f$  (EtOAc:hexane 35:65 v/v) 0.28

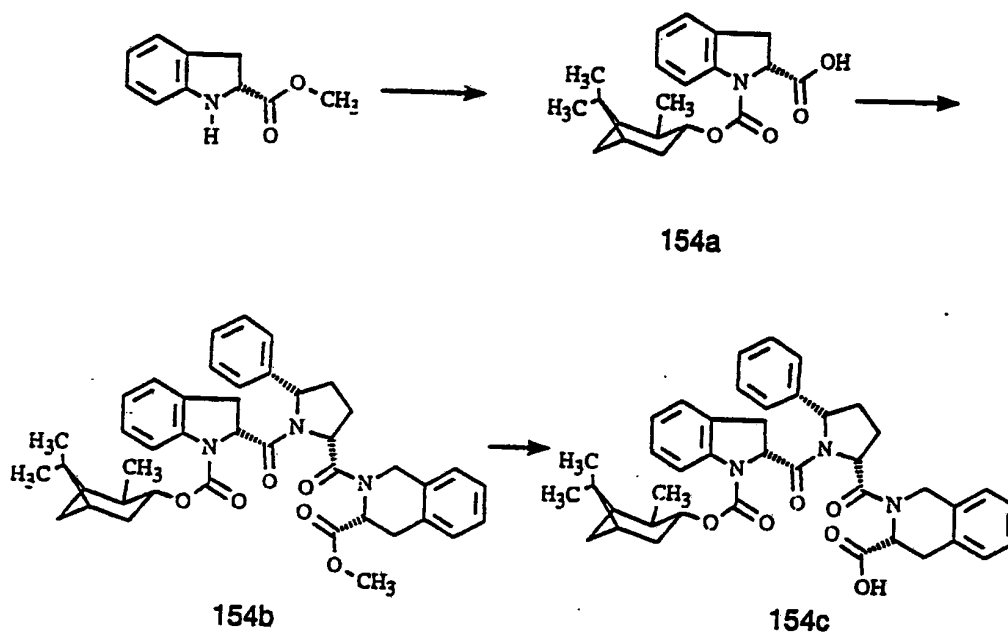
**153c** (3R)-2-[(2R,5S)-1-[(2R)-1-[(1S)-*endo*-Bornyl]oxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **153b** on a 0.19 mmol scale following the method described for **1f**. The product was isolated in 47% yield (62 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

HPLC System B  $t_R$ =20.6' >95%

Mass spec (FAB)  $m/e$ =676  $[M+H]^+$

### EXAMPLE 154



**154a** (2R)-1-[(1R,2R,3R,5S)-Isopinocampheyl]oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from (1R,2R,3R,5S)-isopinocampheol on a 2.34 mmol scale following the method described for **72a**. The product was isolated in 57% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).



**154b**                      Methyl                      (3R)-2-((2R,5S)-1-((2R)-1-((1R,2R,3R,5S)-isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 68a and 154a on a 0.28 mmol scale following the method described for 79d. The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R<sub>f</sub> (EtOAc:hexane 35:65 v/v) 0.28

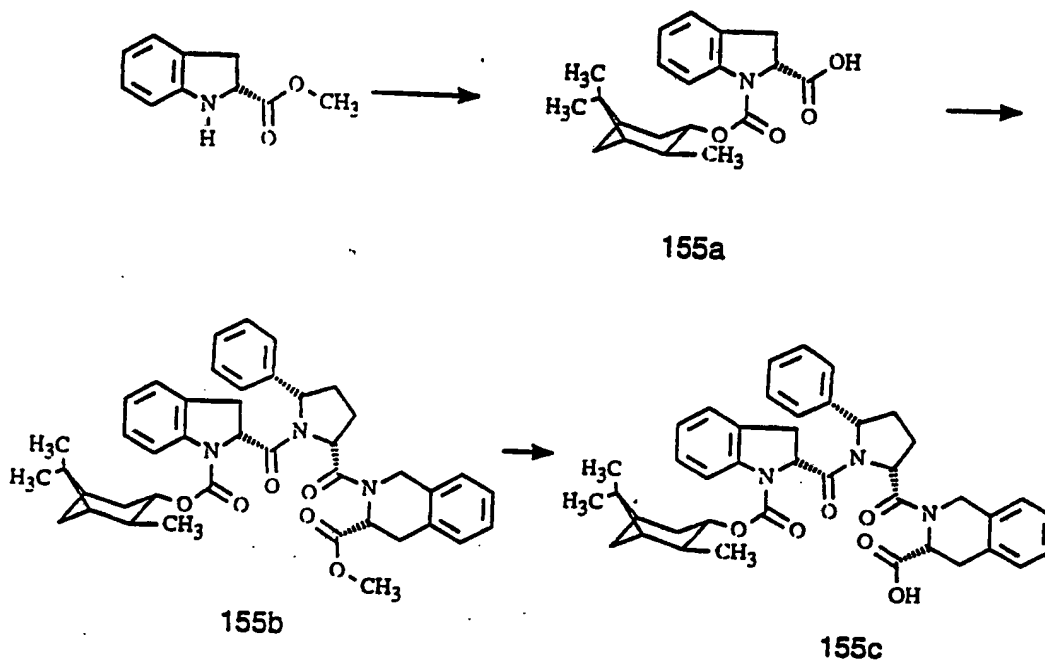
**154c**    (3R)-2-((2R,5S)-1-((2R)-1-((1R,2R,3R,5S)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 154b on a 0.20 mmol scale following the method described for 1f. The product was isolated in 53% yield (73 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

HPLC System B t<sub>R</sub>=21.0' >95%

Mass spec (FAB) m/e=676 [M+H]<sup>+</sup>

## EXAMPLE 155



**155a** (2R)-1-((1S,2S,3S,5R)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from (1S,2S,3S,5R)-isopinocampheol on a 2.34 mmol scale following the method described for 72a. The product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).

**155b** Methyl (3R)-2-((2R,5S)-1-((2R)-1-((1S,2S,3S,5R)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 68a and 155a on a 0.28 mmol scale following the method described for 79d. The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R<sub>f</sub> (EtOAc:hexane 35:65 v/v) 0.27

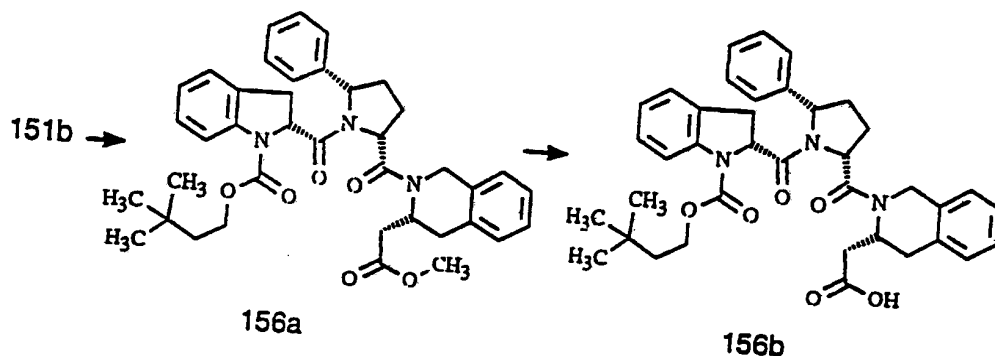
**155c** (3R)-2-((2R,5S)-1-((2R)-1-((1S,2S,3S,5R)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 155b on a 0.21 mmol scale following the method described for 1f. The product was isolated in 39% yield (56 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

HPLC System B t<sub>R</sub>=21.3' >98%

Mass spec (FAB) m/e=676 [M+H]<sup>+</sup>

## EXAMPLE 156



**156a** Methyl (3R)-2-[(2R,5S)-1-[(2R)-1-(3,3-dimethylbutyl)oxycarbonyl]-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 78a and 151a on a 0.30 mmol scale following the method described for 79d. The product was isolated in 77% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

$R_f$  (EtOAc:hexane 50:50 v/v) 0.49

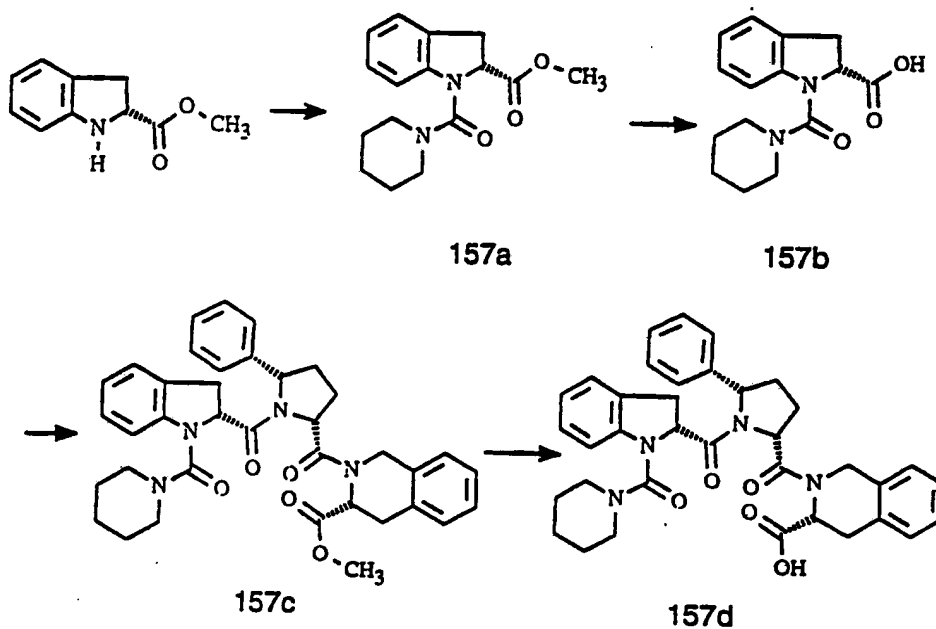
**156b** (3R)-2-[(2R,5S)-1-[(2R)-1-(3,3-Dimethylbutyl)oxycarbonyl]-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 156a on a 0.23 mmol scale following the method described for 1f. The product was isolated in 44% yield (65 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

HPLC System B  $t_R$ =19.0' >98%

Mass spec (FAB)  $m/e$ =660  $[M+Na]^+$

## EXAMPLE 157



**157a Methyl (2R)-1-(1-piperidino)carbonyl-2,3-dihydroindole-2-carboxylate.**

This was prepared from piperidine on a 1.64 mmol scale following the method described for 72a but without the final hydrolysis. The product was isolated in 44% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

$R_f$  (EtOAc:hexane 30:70 v/v) 0.14

**157b (2R)-1-(1-Piperidino)carbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from 157a on a 0.71 mmol scale following the method described for 1f. The product was isolated in 72% yield and used without purification.

**157c Methyl (3R)-2-((2R,5S)-1-((2R)-1-(1-piperidino)carbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 68a and 157b on a 0.51 mmol scale following the method described for 79d. The product was isolated in 54% yield after flash chromatography on silica gel (eluant EtOAc:hexane 70:30 v/v).

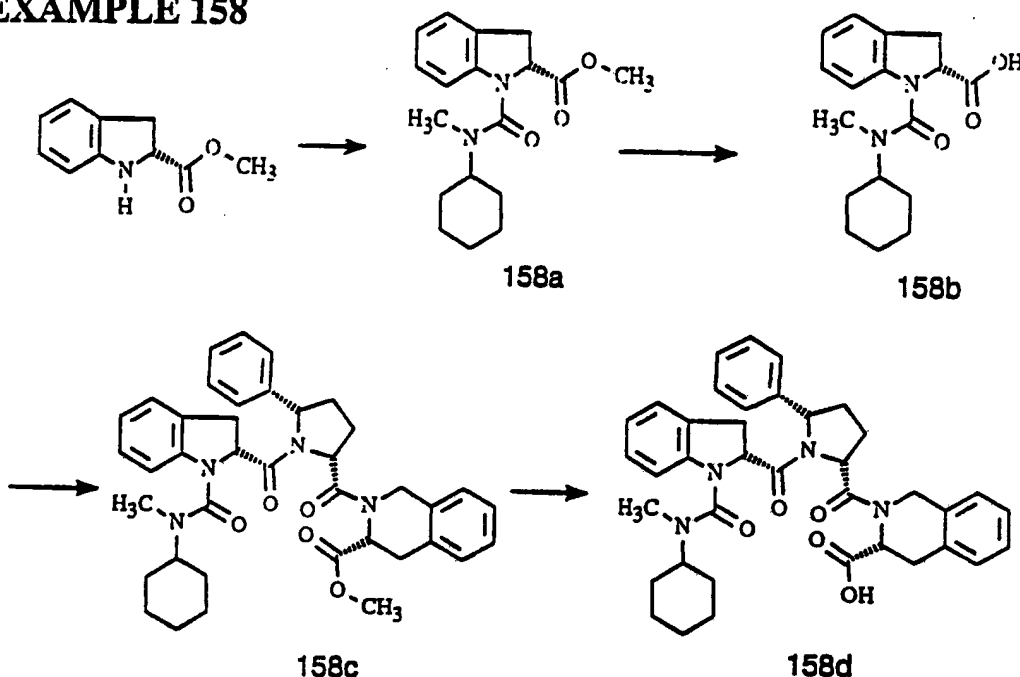
$R_f$  (EtOAc:hexane 70:30 v/v) 0.16

**157d (3R)-2-((2R,5S)-1-((2R)-1-(1-Piperidino)carbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 157c on a 0.28 mmol scale following the method described for 1f. The product was isolated in 18% yield (30 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System B  $t_R$ =14.9' >98%

Mass spec (FAB)  $m/e$ =607  $[M+H]^+$

**EXAMPLE 158**

**158a Methyl (2R)-1-(N-cyclohexyl-N-methylcarbamoyl)-2,3-dihydroindole-2-carboxylate.**

This was prepared from N-methyl-cyclohexylamine on a 1.64 mmol scale following the method described for 157a. The product was isolated in 25% yield after flash chromatography on silica gel (eluant EtOAc:hexane 15:85 v/v).

$R_f$  (EtOAc:hexane 30:70 v/v) 0.20

**158b (2R)-1-(N-Cyclohexyl-N-methylcarbamoyl)-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from 158a on a 0.60 mmol scale following the method described for 1f. The product was isolated in 67% yield and used without purification.

**158c Methyl (3R)-2-((2R,5S)-1-((2R)-1-(N-cyclohexyl-N-methylcarbamoyl)-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 68a and 158b on a 0.40 mmol scale following the method described for 79d. The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v).

$R_f$  (EtOAc:hexane 70:30 v/v) 0.25

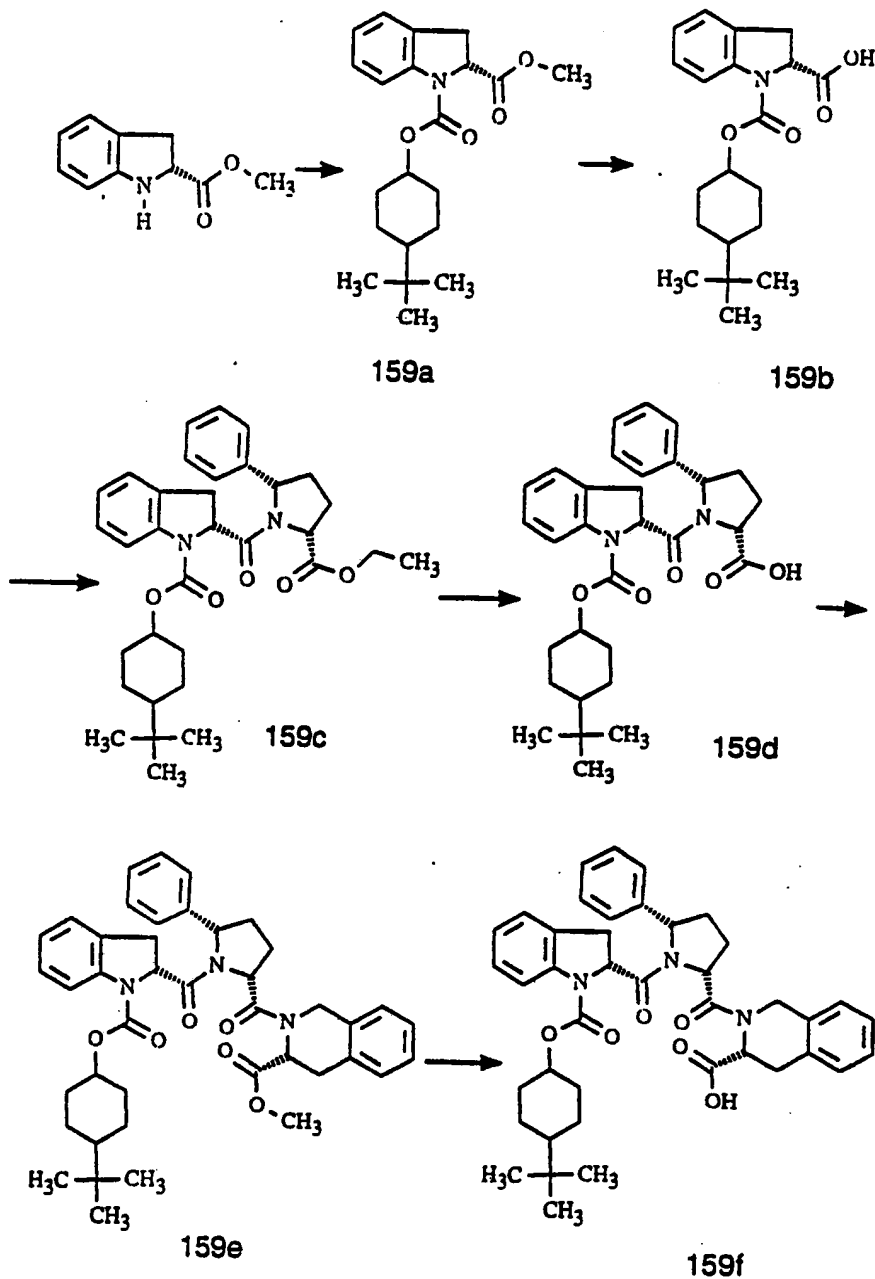
158d (3R)-2-((2R,5S)-1-((2R)-1-(N-Cyclohexyl-N-methylcarbamoyl)-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 158c on a 0.29 mmol scale following the method described for 1f. The product was isolated in 33% yield (60 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 85:15:2 v/v/v).

HPLC System B  $t_R$ =17.6' >99%

Mass spec (FAB)  $m/e$ =635  $[M+H]^+$

## EXAMPLE 159



**159a** Methyl (2R)-1-(4-*tert*-butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylate.

This was prepared from 4-*tert*-butylcyclohexanol on a 1.64 mmol scale following the method described for 157a. The product was isolated in 50% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 20:80:2 v/v/v).

**159b (2R)-1-(4-*tert*-Butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from 159a on a 0.82 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**159c Ethyl (2R,5S)-1-((2R)-1-(4-*tert*-butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylate.**

This was prepared from 30a and 159b on a 0.82 mmol scale following the method described for 1d. The product was isolated in 34% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

$R_f$  (EtOAc:hexane 40:60 v/v) 0.46

**159d (2R,5S)-1-((2R)-1-(4-*tert*-Butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylic acid.**

This was prepared from 159c on a 0.28 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**159e Methyl (3R)-2-((2R,5S)-1-((2R)-1-(4-*tert*-butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 26a and 159d on a 0.28 mmol scale following the method described for 1d. The product was isolated in 93% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

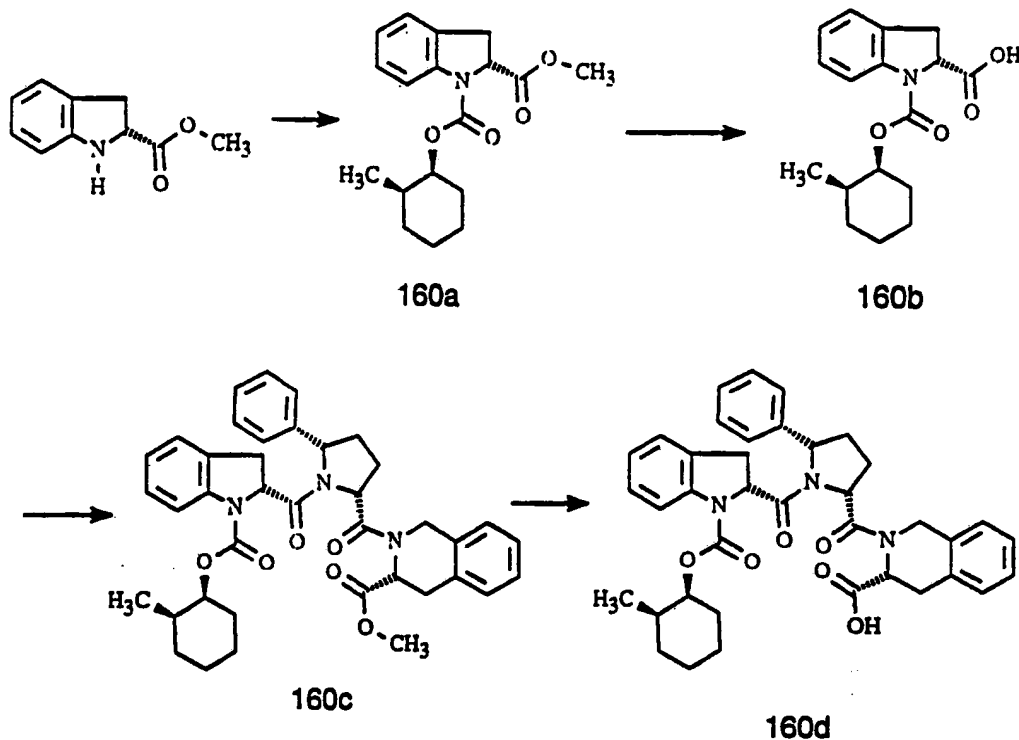
**159f (3R)-2-((2R,5S)-1-((2R)-1-(4-*tert*-Butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 159e on a 0.26 mmol scale following the method described for 1f. The product was isolated in 35% yield (62 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:2 v/v/v).

HPLC System B  $t_R$ =23.0' >95%

Mass spec (FAB)  $m/e$ =678  $[M+H]^+$



**EXAMPLE 160**

**160a** Methyl (2R)-1-(2-*cis*-methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylate.

This was prepared from (±)-2-*cis*-methylcyclohexanol on a 3.28 mmol scale following the method described for 157a. The product was isolated in 51% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

$R_f$  (EtOAc:hexane 30:70 v/v) 0.41

**160b** (2R)-1-(2-*cis*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from 160a on a 1.66 mmol scale following the method described for 1f. The product was isolated in 23% yield and used without purification.

**160c** Methyl (3R)-2-((2R,5S)-1-((2R)-1-(2-*cis*-methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylate)-5-phenylpyrrolidine-2-carboxylate)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 68a and 160b on a 0.38 mmol scale following the method described for 79d. The product was isolated in 25% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 25:75:1 v/v/v).

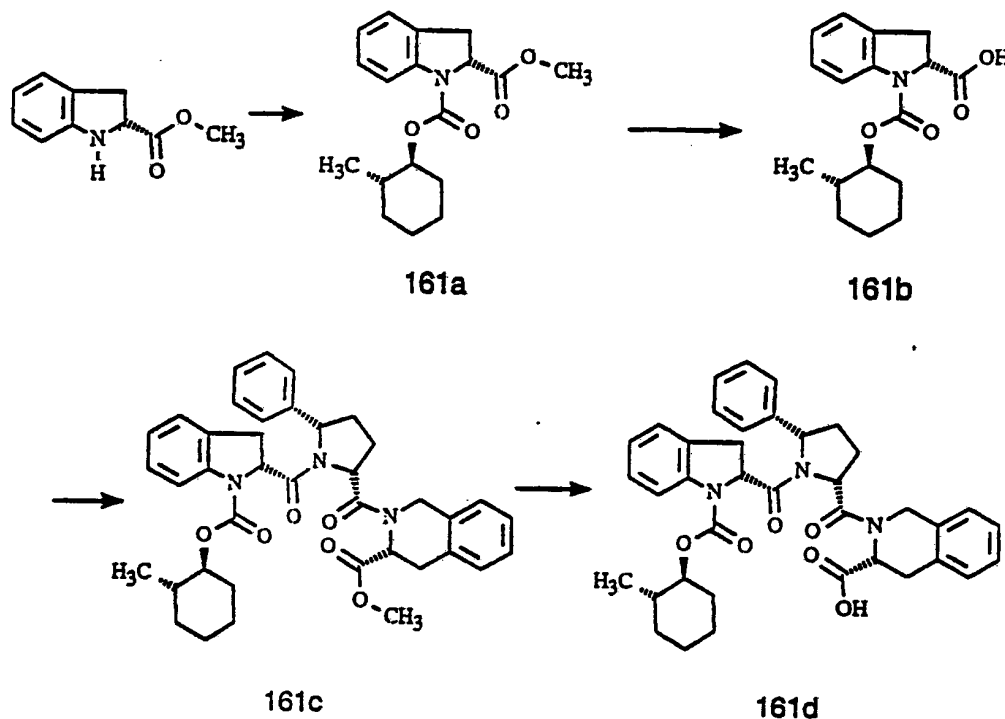
**160d** (3R)-2-((2R,5S)-1-((2R)-1-(2-*cis*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 160c on a 0.09 mmol scale following the method described for 1f. The product was isolated in 48% yield (29 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:2 v/v/v).

HPLC System A  $t_R$ =18.0' >98%

Mass spec (FAB)  $m/e$ =636 [M+H]<sup>+</sup>

### EXAMPLE 161



**161a** Methyl (2R)-1-(2-*trans*-methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylate.

This was prepared from (±)-2-*trans*-methylcyclohexanol on a 1.64 mmol scale following the method described for 157a. The product was isolated in 28% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

$R_f$  (EtOAc:hexane 30:70 v/v) 0.41

**161b (2R)-1-(2-*trans*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from 161a on a 0.45 mmol scale following the method described for 1f. The product was isolated in 44% yield and used without purification.

**161c Methyl (3R)-2-((2R,5S)-1-((2R)-1-(2-*trans*-methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

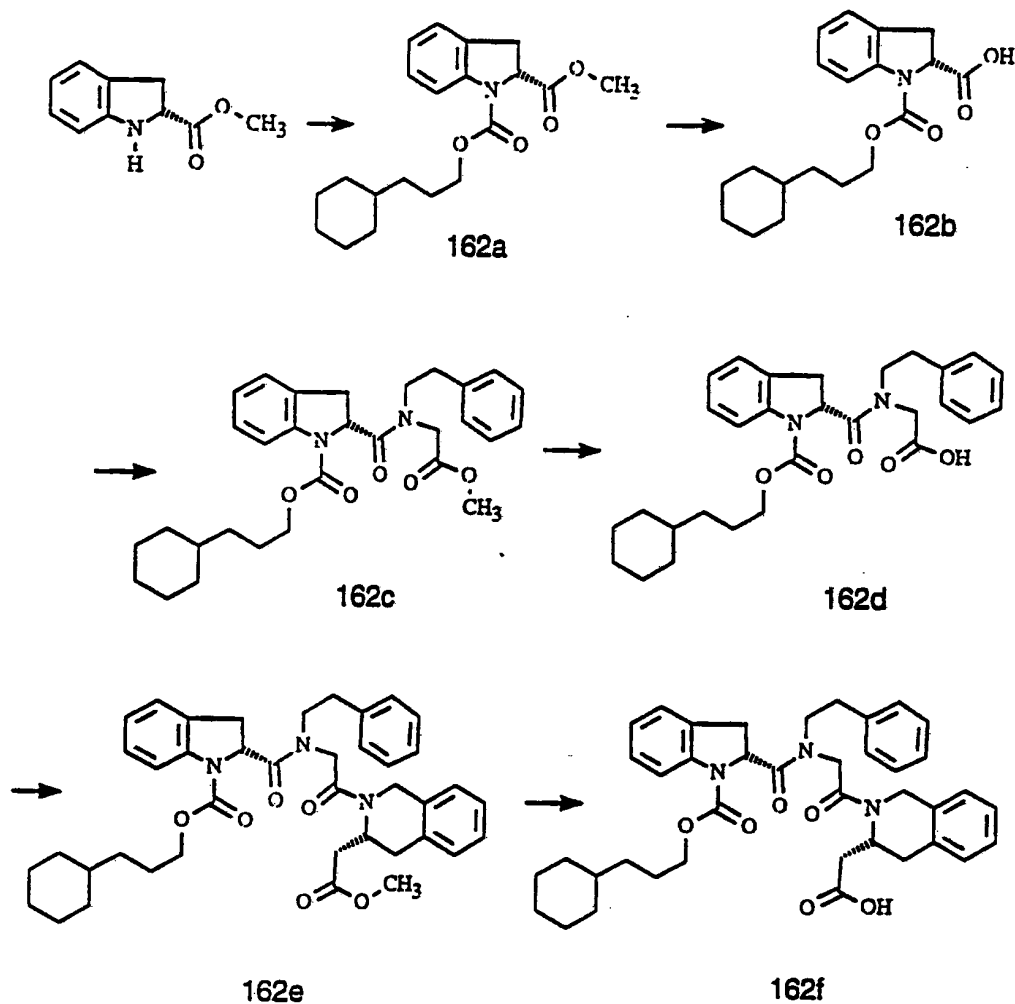
This was prepared from 68a and 161b on a 0.20 mmol scale following the method described for 79d. The product was isolated in 42% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 25:75:1 v/v/v).

**161d (3R)-2-((2R,5S)-1-((2R)-1-(2-*trans*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 161c on a 0.08 mmol scale following the method described for 1f. The product was isolated in 38% yield (20 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:2 v/v/v).

HPLC System B  $t_R$ =18.4' >98%

Mass spec (FAB)  $m/e$ =636 [M+H]<sup>+</sup>

**EXAMPLE 162**

**162a** Methyl (2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carboxylate.

This was prepared from 3-cyclohexylpropanol on a 1.64 mmol scale following the method described for 157a. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

$R_f$  (EtOAc:hexane 30:70 v/v) 0.49

**162b** (2R)-1-(3-Cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from 162a on a 1.64 mmol scale following the method described for 1f. The product was isolated in 60% yield and used without purification.

**162c** Methyl N-phenethyl-N-((2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from 32a and 162b on a 0.99 mmol scale following the method described for 1d. The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:1 v/v/v).

**162d** N-Phenethyl-N-((2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from 162c on a 0.81 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**162e** Methyl (3R)-2-(N-phenethyl-N-((2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c and 162d on a 0.81 mmol scale following the method described for 1d. The product was isolated in 63% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.34

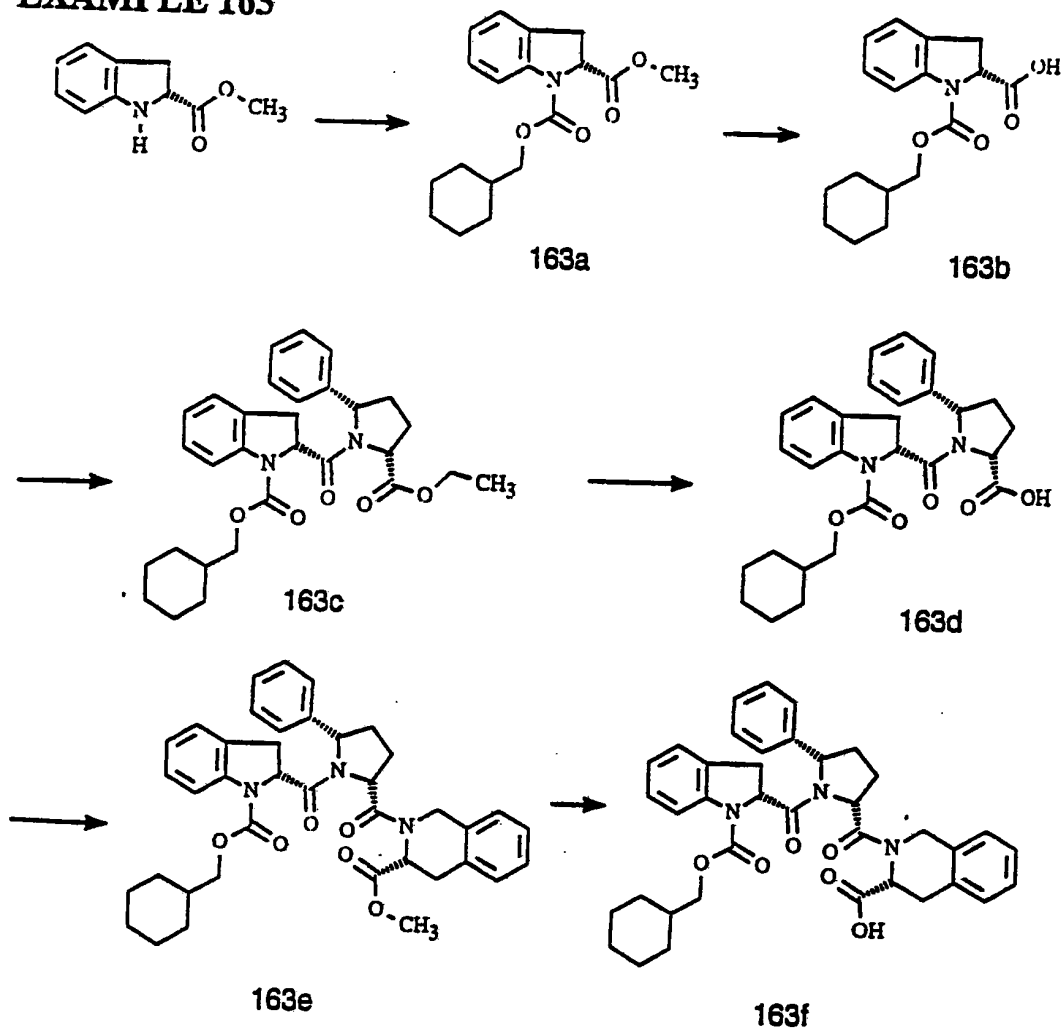
**162f** (3R)-2-(N-Phenethyl-N-((2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 162e on a 0.51 mmol scale following the method described for 1f. The product was isolated in 51% yield (161 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

HPLC System B t<sub>R</sub>=21.5' >98%

Mass spec (FAB) m/e=688 [M+Na]<sup>+</sup>

224

**EXAMPLE 163****163a Methyl (2R)-1-cyclohexylmethoxycarbonyl-2,3-dihydroindole-2-carboxylate.**

This was prepared from cyclohexanemethanol on a 1.64 mmol scale following the method described for 157a. The product was isolated in 78% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

$R_f$  (EtOAc:hexane 30:70 v/v) 0.49

**163b (2R)-1-Cyclohexylmethoxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from 163a on a 1.27 mmol scale following the method described for 1f. The product was isolated in 55% yield and used without purification.

**163c Ethyl (2R,5S)-1-((2R)-1-cyclohexylmethyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylate.**

This was prepared from 30a and 163b on a 0.70 mmol scale following the method described for 1d. The product was isolated in 57% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 25:75:1 v/v/v).

**163d (2R,5S)-1-((2R)-1-Cyclohexylmethyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylic acid.**

This was prepared from 163c on a 0.40 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**163e Methyl (3R)-2-((2R,5S)-1-((2R)-1-cyclohexylmethyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 26a and 163d on a 0.40 mmol scale following the method described for 1d. The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

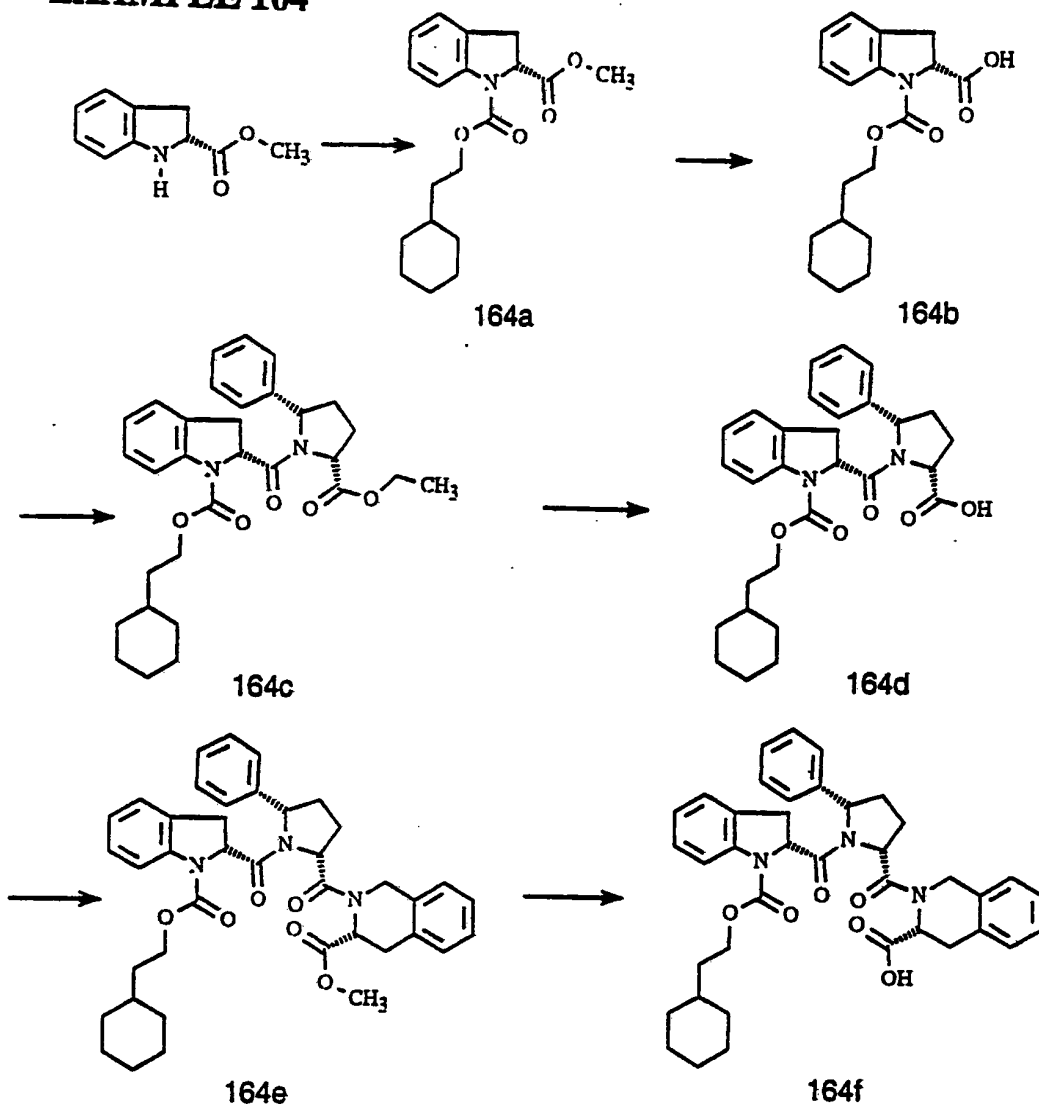
$R_f$  (EtOAc:hexane 50:50 v/v) 0.40

**163f (3R)-2-((2R,5S)-1-((2R)-1-Cyclohexylmethyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 163e on a 0.25 mmol scale following the method described for 1f. The product was isolated in 16% yield (24 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:2 v/v/v).

HPLC System B  $t_R$ =18.8' >98%

Mass spec (FAB)  $m/e$ =636  $[M+H]^+$

**EXAMPLE 164**

**164a Methyl (2R)-1-(2-cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carboxylate.**

This was prepared from 2-cyclohexylethanol on a 1.64 mmol scale following the method described for 157a. The product was isolated in 91% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

$R_f$  (EtOAc:hexane 30:70 v/v) 0.54

**164b (2R)-1-(2-Cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.**

This was prepared from 164a on a 1.50 mmol scale following the method described for 1f. The product was isolated in 55% yield and used without purification.



**164c Ethyl (2R,5S)-1-((2R)-1-(2-cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylate.**

This was prepared from 30a and 164b on a 0.82 mmol scale following the method described for 1d. The product was isolated in 56% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 25:75:1 v/v/v).

**164d (2R,5S)-1-((2R)-1-(2-Cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylic acid.**

This was prepared from 164c on a 0.46 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**164e Methyl (3R)-2-((2R,5S)-1-((2R)-1-(2-cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

This was prepared from 26a and 164d on a 0.46 mmol scale following the method described for 1d. The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

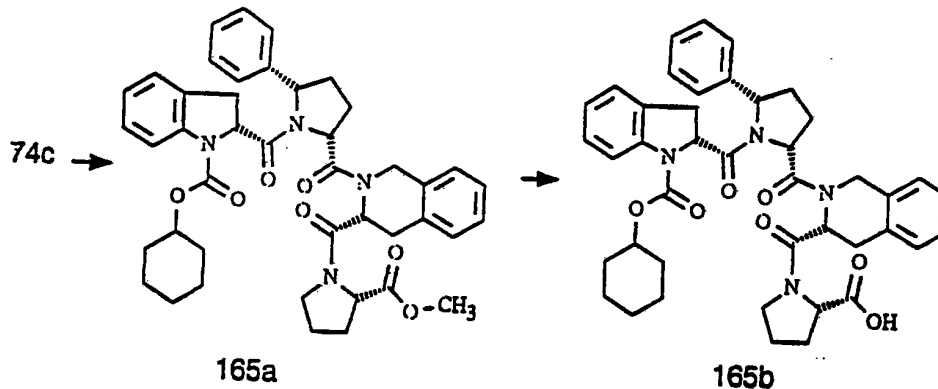
R<sub>f</sub> (EtOAc:hexane 50:50 v/v) 0.40

**164f (3R)-2-((2R,5S)-1-((2R)-1-(2-Cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 164e on a 0.33 mmol scale following the method described for 1f. The product was isolated in 16% yield (33 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:2 v/v/v).

HPLC System B t<sub>R</sub>=21.8' >90%

Mass spec (FAB) m/e=650 [M+H]<sup>+</sup>

**EXAMPLE 165**

**165a** Methyl N-[(3R)-2-[(2R,5S)-1-[(2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-5-phenylpyrrolidine-2-carboxyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxyl]-proline.

This was prepared from 74c and ProOMe on a 0.08 mmol scale following the method described for 1d. The product was used without purification, assuming a yield of 100%.  $R_f$  (EtOAc:pet. ether 70:30 v/v) 0.22

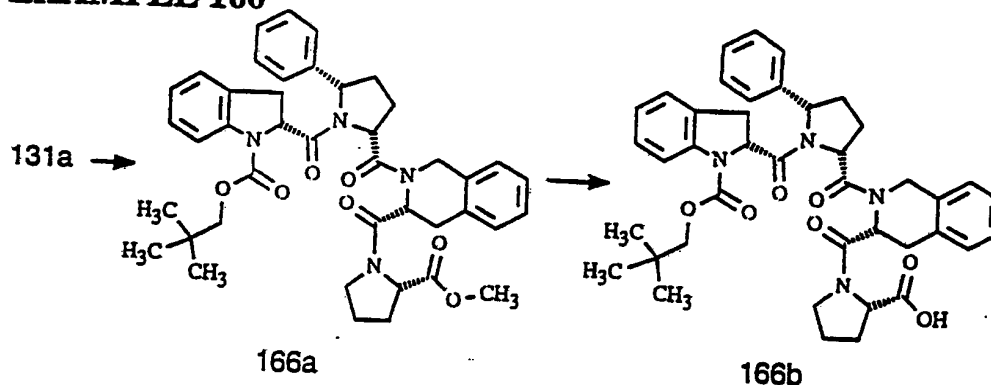
**165b** N-[(3R)-2-[(2R,5S)-1-[(2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carboxyl)-5-phenylpyrrolidine-2-carboxyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxyl]-proline.

This was prepared from 165a on a 0.08 mmol scale following the method described for 1f. The product was isolated in 57% yield (31 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:1 v/v).

HPLC System A  $t_R$ =15.5' >98%

AAA Peptide content=83%

Mass spec (FAB)  $m/e$ =604, 272

**EXAMPLE 166**

**166a** Methyl N-((3R)-2-((2R,5S)-1-((2R)-1-neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-proline.

This was prepared from 131a on a 0.30 mmol scale following the method described for 81a. The product was isolated in 32% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

**166b** N-((3R)-2-((2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-proline.

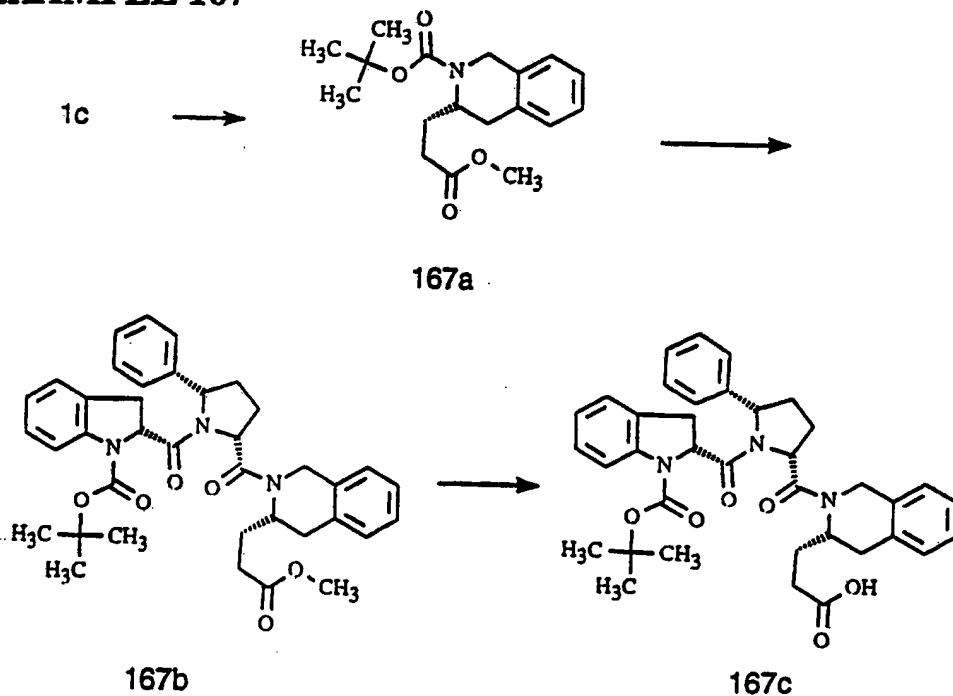
This was prepared from 166a on a 0.10 mmol scale following the method described for 1f. The product was isolated in 89% yield (61 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:1 v/v).

HPLC System A  $t_R$ =15.1' >98%

AAA Peptide content=76%

Mass spec (FAB)  $m/e$ =592, 272

### EXAMPLE 167



**167a Methyl (3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-propanoate.**

This was prepared from 1b on a 3.6 mmol scale. The ester was hydrolysed following the method described for 1f to give the corresponding acid which was then homologated following the method described for 1b. The intermediate diazoketone was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v) and the title product was isolated in 22% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

R<sub>f</sub> (EtOAc:pet. ether 10:90 v/v) 0.12

<sup>1</sup>H NMR δ 1.49 (9H,s); 1.6 - 1.9 (2H,m); 2.3 (2H,m); 2.63 (1H,dd,J=16.2 Hz); 3.09 (1H,dd,J=16.6 Hz); 3.64 (3H,s); 4.2 (1H,br); 4.6 (1H,br); 4.9 (1H,br); 7.0 - 7.2 (4H,m)

**167b Methyl (3R)-2-((2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-propanoate.**

This was prepared from 79b and 167a on a 0.39 mmol scale following the method described for 79d. The product was isolated in 71% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

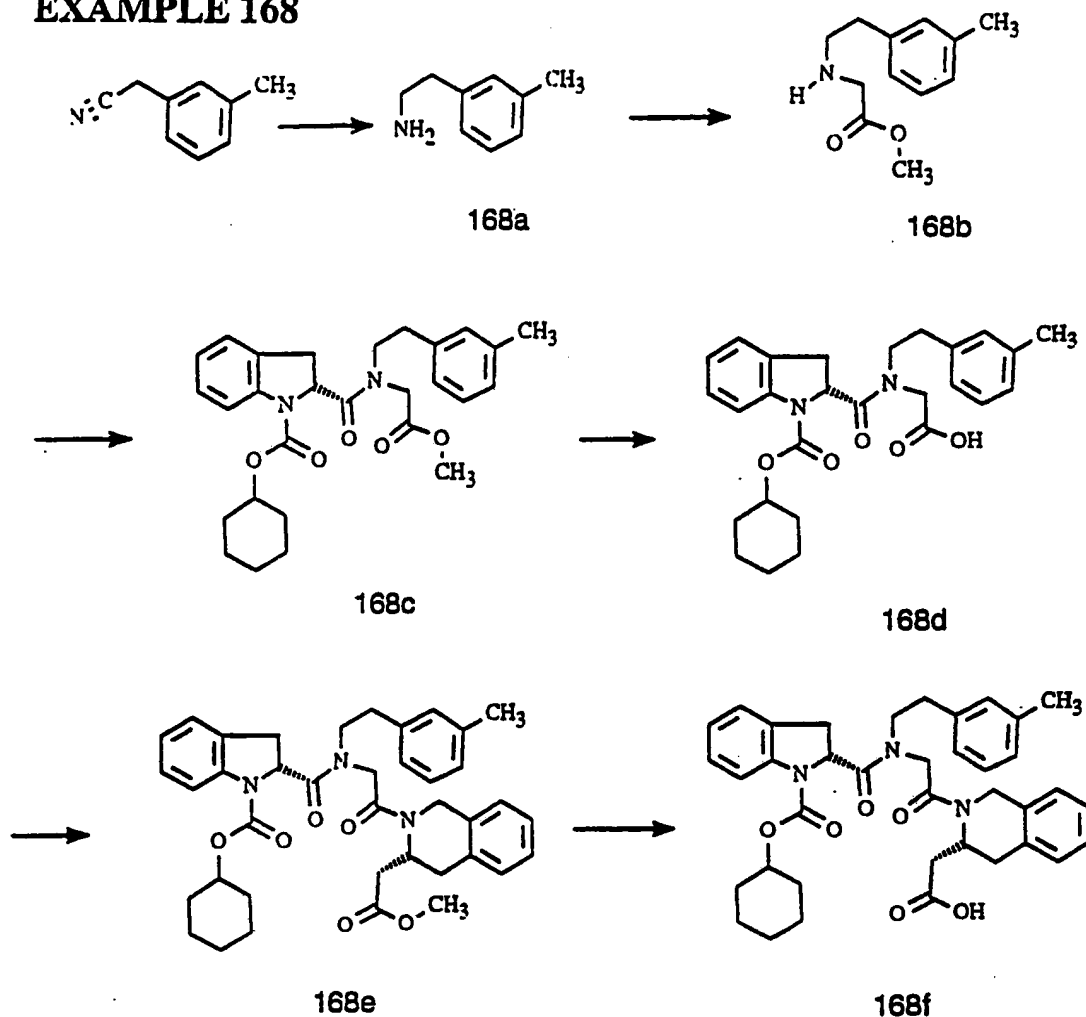
R<sub>f</sub> (EtOAc:pet. ether 30:70 v/v) 0.13

**167c (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-propanoic acid.**

This was prepared from 167b on a 0.28 mmol scale following the method described for 1f. The product was isolated in 74% yield (130 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:1 v/v/v).

HPLC System A t<sub>R</sub>=15.4' >98%

Mass spec (FAB) m/e=624 [M+H]<sup>+</sup>

**EXAMPLE 168****168a 3-Methylphenethylamine.**

To a stirred solution of 3-methylbenzyl cyanide (1 g, 7.6 mmol) and  $\text{CoCl}_2$  (0.49 g, 3.8 mmol) in MeOH (20 mL) was added  $\text{NaBH}_4$  (1.2 g, 30.4 mmol) portionwise at room temperature. The mixture was stirred for 30 min then poured onto crushed ice. 10% Aq.  $\text{KHSO}_4$  was added until the mixture was strongly acidic (pH 2), and the insoluble material was removed by filtration through Celite. The filtrate was treated with NaOH pellets until basic (pH 10) and extracted once with EtOAc, then twice with  $\text{CH}_2\text{Cl}_2$ . The separate extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , combined and evaporated to give the title compound (0.60 g, 59%) which was used without purification.

**168b Methyl N-3-methylphenethyl-glycinate.**

This was prepared from 168a on a 4.45 mmol scale following the method described for 32a. The product was isolated in 6% yield after flash chromatography on silica gel (eluant EtOAc).

**168c Methyl N-3-methylphenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 74a and 168b on a 0.26 mmol scale following the method described for 1d. The product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**168d N-3-Methylphenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 168c on a 0.18 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**168e Methyl (3R)-2-{N-3-methylphenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

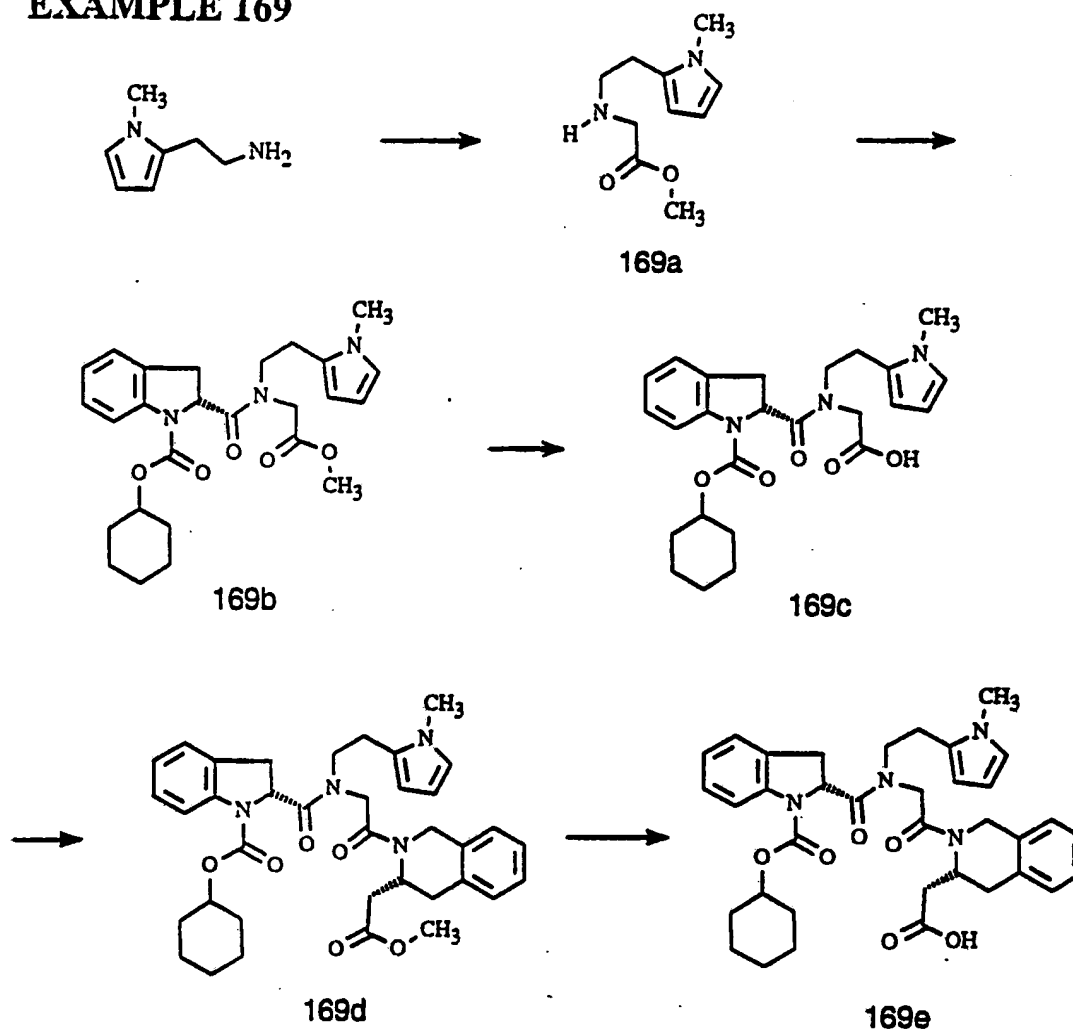
This was prepared from 1c and 168d on a 0.18 mmol scale following the method described for 1d. The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**168f (3R)-2-{N-3-Methylphenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 168e on a 0.13 mmol scale following the method described for 1f. The product was isolated in 72% yield (60 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:1 v/v/v).

HPLC System A  $t_R$ =17.1' >98%

Mass spec (FAB)  $m/e$ =660  $[M+Na]^+$

**EXAMPLE 169****169a Methyl N-(2-(1-Methylpyrrol-2-yl)ethyl)-glycinate.**

This was prepared from 2-(1-methylpyrrol-2-yl)ethan-1-amine on a 8.0 mmol scale following the method described for 32a. The product was isolated in 27% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 70:30 then EtOAc).

**169b Methyl N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 74a and 169a on a 2.16 mmol scale following the method described for 1d. The product was isolated in 34% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

**169c**            **N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 169b on a 0.73 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**169d**            **Methyl            (3R)-2-{N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 1c and 169c on a 0.73 mmol scale following the method described for 1d. The product was isolated in 58% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

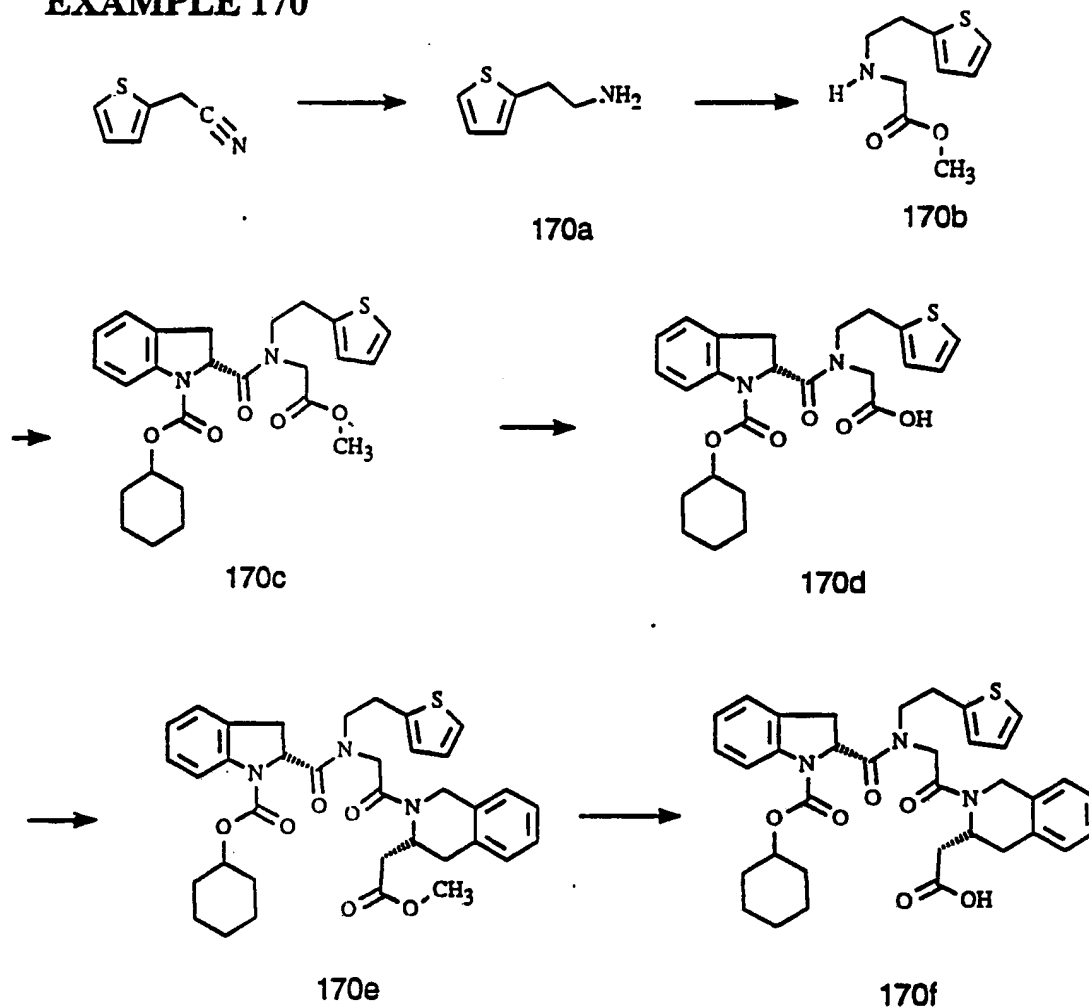
**169e**            **(3R)-2-{N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 169d on a 0.42 mmol scale following the method described for 1f. The product was isolated in 75% yield (197 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 80:20:2 v/v/v).

HPLC System A  $t_R$ =15.0' >98%

Mass spec (FAB)  $m/e$ =627 [M+H]<sup>+</sup>



**EXAMPLE 170****170a (2-Thienyl)ethylamine.**

This was prepared from 2-thienylacetonitrile on an 18.6 mmol scale following the method described for 168a. The product was isolated in 32% yield and used without purification.

**170b Methyl N-(2-thienyl)ethyl-glycinate.**

This was prepared from 170a on a 5.96 mmol scale following the method described for 32a. The product was isolated in 35% yield after flash chromatography on silica gel (eluant  $\text{CHCl}_3:\text{MeOH}:\text{AcOH}$  30:2:1 v/v/v).

**170c Methyl N-(2-thienyl)ethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 74a and 170b on a 1.05 mmol scale following the method described for 1d. The product was isolated in 71% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**170d N-(2-Thienyl)ethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 170c on a 0.75 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**170e Methyl (3R)-2-{N-(2-thienyl)ethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

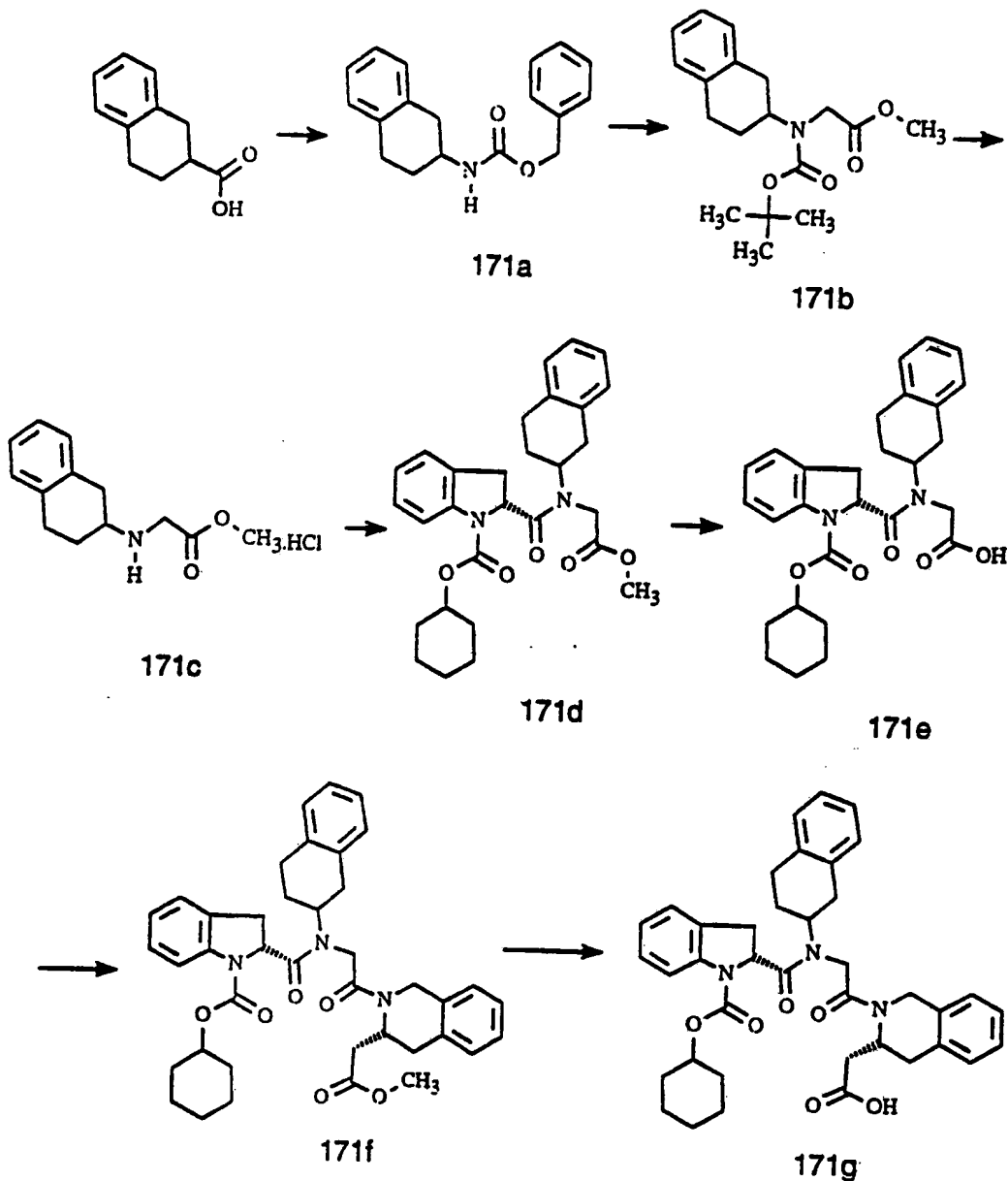
This was prepared from 1c and 170d on a 0.75 mmol scale following the method described for 1d. The product was isolated in 59% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

**170f (3R)-2-{N-(2-Thienyl)ethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 170e on a 0.44 mmol scale following the method described for 1f. The product was isolated in 57% yield (157 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 80:20:1 v/v/v).

HPLC System A  $t_R$ =14.8' >98%

Mass spec (FAB)  $m/e$ =493 [M+H]<sup>+</sup>

**EXAMPLE 171****171a (2*RS*)-2-Benzyloxycarbonylamino-1,2,3,4-tetrahydronaphthalene.**

To a stirred solution of 1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (3 g, 17 mmol) and N-methylmorpholine (2.1 mL, 18.7 mmol) under  $N_2$  was added  $(PhO)_2P(O)N_3$  (4 mL, 18.7 mmol) and the mixture was heated at reflux for 2.5 hr then cooled to room temperature. Benzyl alcohol (3.7 mL, 34 mmol) was added and the solution was heated at reflux overnight, cooled to room temperature, and concentrated *in vacuo*. The residue was taken up in EtOAc and washed successively with aq.  $KHSO_4$ ,  $KHCO_3$  (twice), water and

brine, filtered (Whatman 1PS phase separator) and concentrated. The product was isolated in 57% yield (4.07 g) after flash chromatography on silica gel (eluant EtOAc:pet. ether 10:90 v/v)

**171b Methyl N-((2RS)-1,2,3,4-tetrahydronaphth-2-yl)-N-tert-butyloxycarbonyl-glycinate.**

This was prepared from 171a on a 7.1 mmol scale in three steps. The amine was deprotected by catalytic hydrogenolysis over 5% Pd-on-carbon, then alkylated following the method described for 32a and finally reprotected with BOC<sub>2</sub>O following the method described for 141c (second part). The product was isolated in 14% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 10:90 v/v).

**171c Methyl N-((2RS)-1,2,3,4-tetrahydronaphth-2-yl)-glycinate hydrochloride.**

This was prepared from 171b on a 1.0 mmol scale following the method described for 1c. The product was used without purification, assuming a yield of 100%.

**171d Methyl N-((2RS)-1,2,3,4-tetrahydronaphth-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 74a and 171c on a 1.0 mmol scale following the method described for 1d. The product was isolated in 48% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**171e N-((2RS)-1,2,3,4-Tetrahydronaphth-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 171d on a 0.48 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**171f Methyl (3R)-2-{N-((2RS)-1,2,3,4-tetrahydronaphth-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 1c and 171e on a 0.48 mmol scale following the method described for 1d. The product was isolated in 52% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

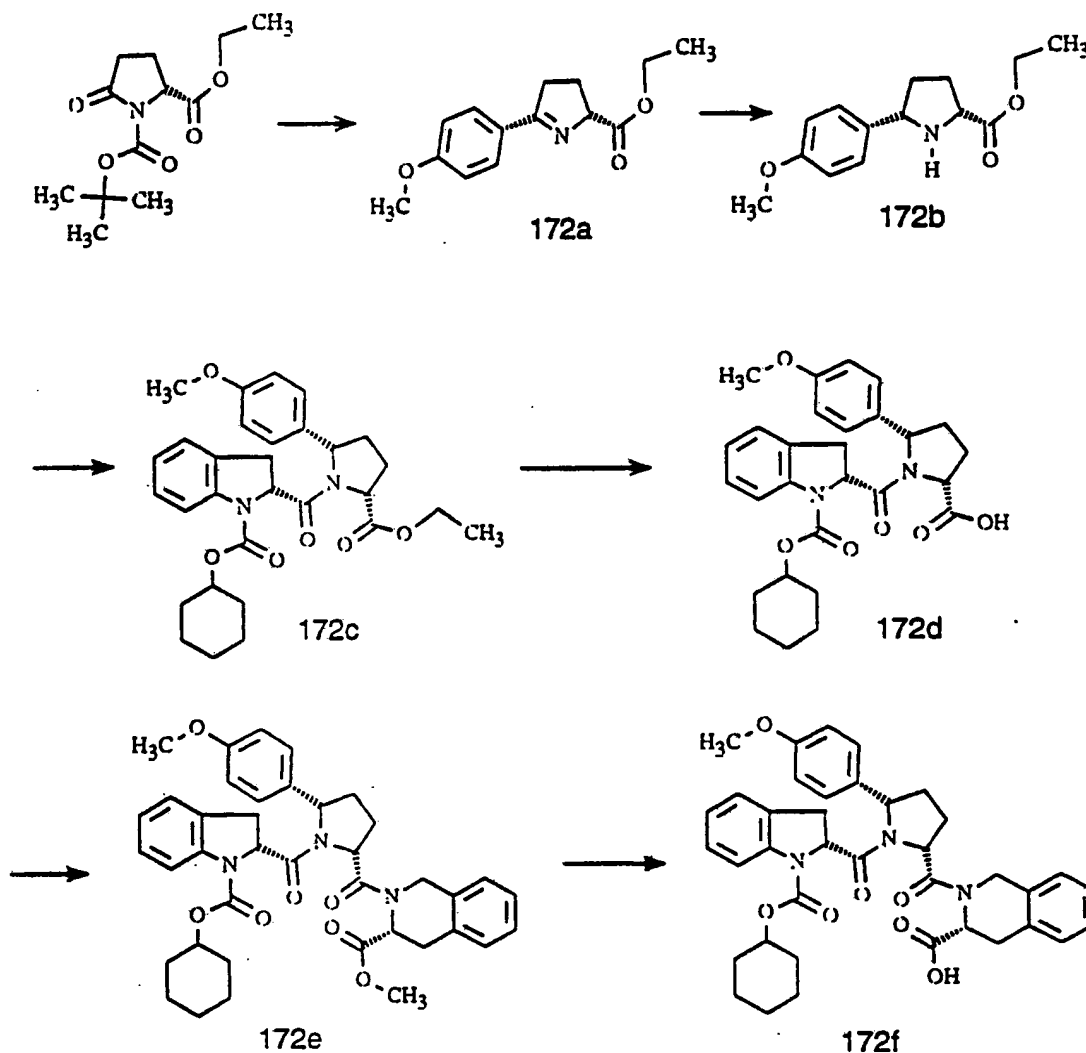
**171g** (3R)-2-{N-((2RS)-1,2,3,4-Tetrahydronaphth-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 171f on a 0.25 mmol scale following the method described for 1f. The product was isolated in 60% yield (97 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:1 v/v/v).

HPLC System A  $t_R$ =16.8' >95%

Mass spec (FAB)  $m/e$ =650  $[M+H]^+$

### EXAMPLE 172



**172a Ethyl (2R)-3,4-dihydro-5-(4-methoxyphenyl)-2H-pyrrole-2-carboxylate.**

This was prepared from 4-methoxyphenylmagnesium bromide on an 8.0 mmol scale following the method described for 87a. The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 then 40:60 v/v).

**172b Ethyl (2R,5S)-5-(4-methoxyphenyl)-pyrrolidine-2-carboxylate.**

This was prepared from 172a on a 6.6 mmol scale following the method described for 30a. The product was isolated in 56% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 then 50:50 v/v).

**172c Ethyl (2R,5S)-1-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(4-methoxyphenyl)-pyrrolidine-2-carboxylate.**

This was prepared from 74a and 172b on a 0.69 mmol scale following the method described for 1d. The product was isolated in 95% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**172d (2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(4-methoxyphenyl)-pyrrolidine-2-carboxylic acid.**

This was prepared from 172c on a 0.65 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**172e Methyl (3R)-2-((2R,5S)-1-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(4-methoxyphenyl)-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.**

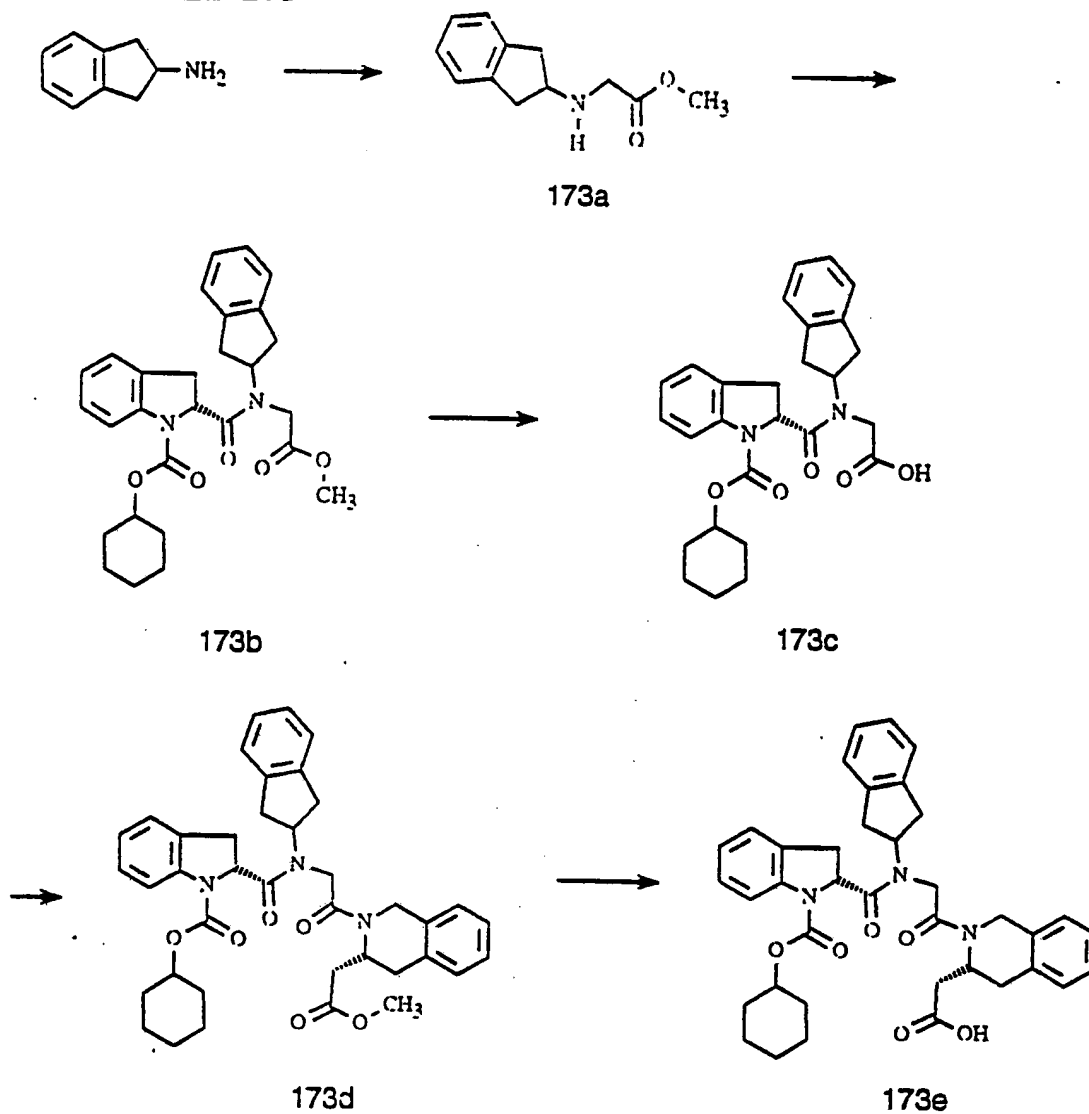
This was prepared from 26a and 172d on a 0.32 mmol scale following the method described for 1d. The product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

**172f (3R)-2-((2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(4-methoxyphenyl)-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.**

This was prepared from 172e on a 0.22 mmol scale following the method described for 1f. The product was isolated in 69% yield (95 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A  $t_R=15.4'$  >98%

Mass spec (FAB)  $m/e=652$   $[M+H]^+$

**EXAMPLE 173****173a Methyl N-(indan-2-yl)-glycinate.**

This was prepared from indan-2-amine on an 8.0 mmol scale following the method described for 32a. The product was isolated in 44% yield after flash chromatography on silica gel (eluant EtOAc).

**173b Methyl N-(indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.**

This was prepared from 74a and 173a on a 0.69 mmol scale following the method described for 1d. The product was isolated in 80% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

**173c N-(Indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.**

This was prepared from 173b on a 0.55 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**173d Methyl (3R)-2-{N-(indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.**

This was prepared from 1c and 173c on a 0.27 mmol scale following the method described for 1d. The product was isolated in 73% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

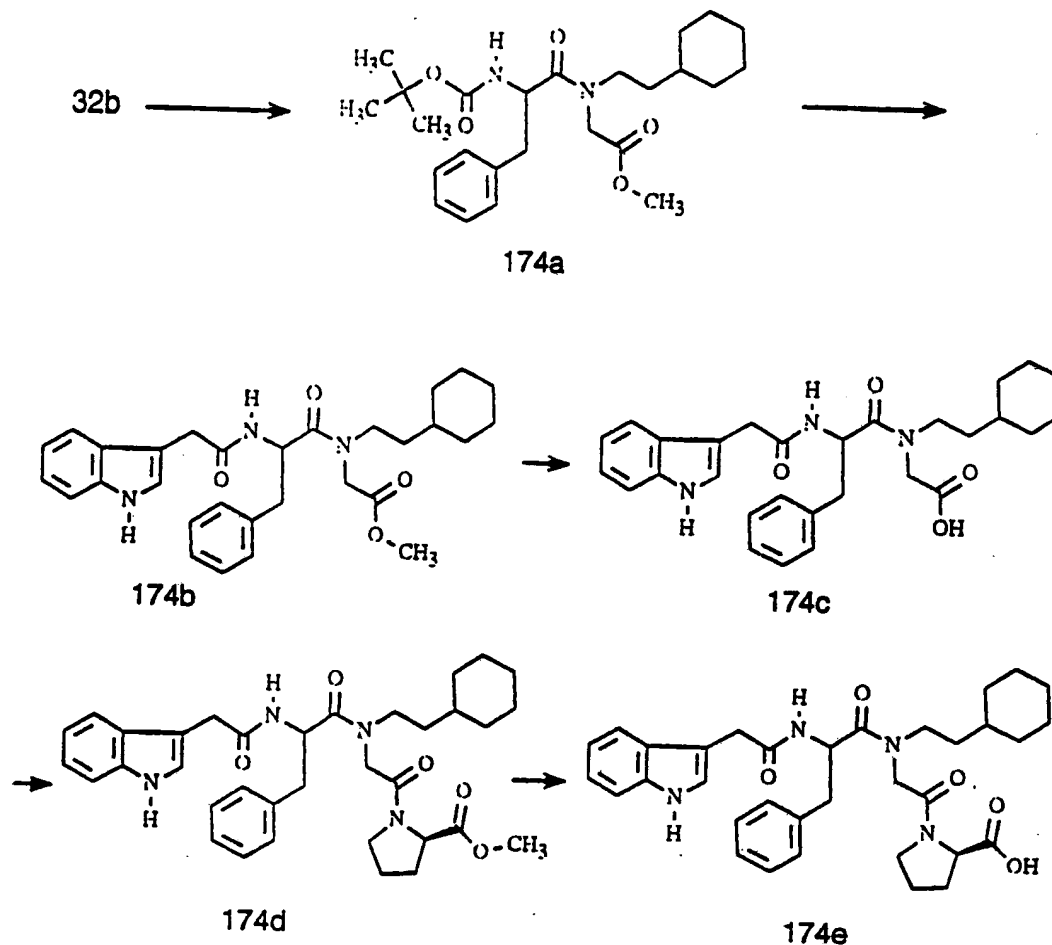
**173e (3R)-2-{N-(Indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 173d on a 0.20 mmol scale following the method described for 1f. The product was isolated in 77% yield (75 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 80:20:2 v/v/v).

HPLC System A  $t_R$ =15.8' >98%

Mass spec (FAB)  $m/e$ =658 [M+H]<sup>+</sup>



**EXAMPLE 174**

**174a** Methyl N-(2-cyclohexylethyl)-N-(N-*tert*-butoxycarbonyl-phenylalanyl)-glycinate.

This was prepared from 32b and BOC-PheOH on a 2.0 mmol scale following the method described for 1d. The product was isolated in 93% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

**174b** Methyl N-(2-cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycinate.

This was prepared from 174a on a 1.86 mmol scale following the method described for 32d. The product was isolated in 52% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 65:35:1 v/v/v).

**174c N-(2-Cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycine.**

This was prepared from 174b on a 0.48 mmol scale following the method described for 34. The product was used without purification, assuming a yield of 100%.

**174d Methyl 1-{N-(2-cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycyl}-D-prolinate.**

This was prepared from 174c and D-ProOMe on a 0.48 mmol scale following the method described for 34. The product was isolated in 42% yield after flash chromatography on silica gel (eluant EtOAc).

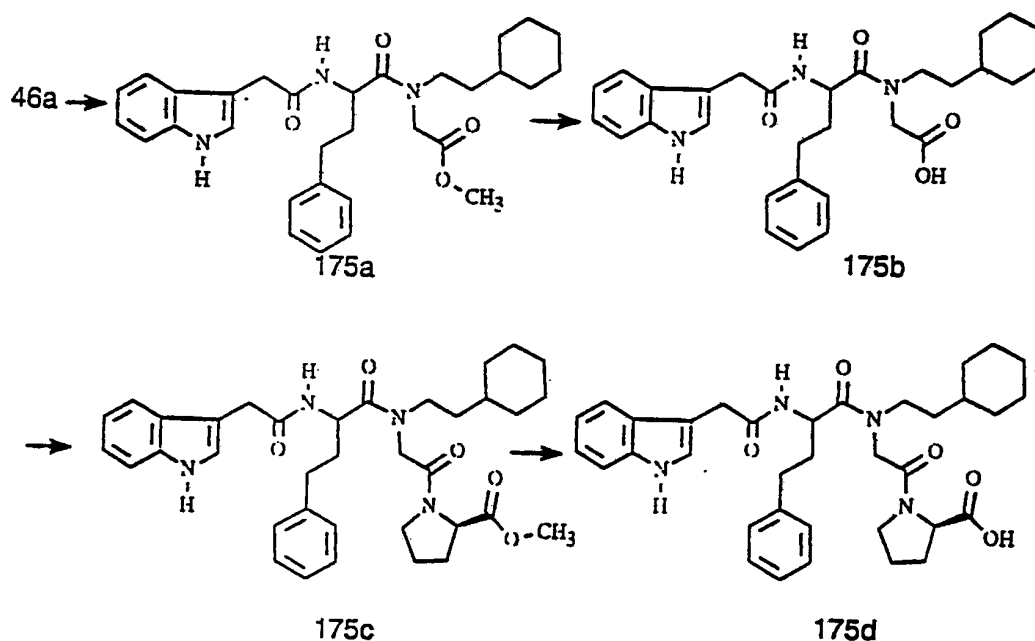
**174e 1-{N-(2-Cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycyl}-D-proline.**

This was prepared from 174d on a 0.20 mmol scale following the method described for 1f. The product was isolated in 61% yield (72 mg) after flash chromatography on silica gel (eluant  $\text{CHCl}_3$ :MeOH:AcOH 35:2:1 v/v/v).

HPLC System B  $t_R$ =10.4' >95%

AAA Phe 0.98: Pro 1.02: Peptide content=87%

Mass spec (FAB)  $m/e$ =587  $[M+H]^+$

**EXAMPLE 175**

**175a Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-4-phenylbutanoyl)-glycinate.**

This was prepared from 46a on a 1.74 mmol scale following the method described for 32d. The product was isolated in 61% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 65:35:1 v/v/v).

**175b N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-4-phenylbutanoyl)-glycine.**

This was prepared from 175a on a 0.53 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

**175c Methyl 1-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-4-phenylbutanoyl)-glycyl}-D-prolinate.**

This was prepared from 175b and D-ProOMe on a 0.53 mmol scale following the method described for 34. The product was isolated in 39% yield after flash chromatography on silica gel (eluant EtOAc).

**175d 1-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl-amino)-4-phenylbutanoyl)-glycyl}-D-proline.**

This was prepared from 175c on a 0.29 mmol scale following the method described for 1f. The product was isolated in 67% yield (116 mg) after flash chromatography on silica gel (eluant CHCl<sub>3</sub>:MeOH:AcOH 35:2:1 v/v/v).

HPLC System B  $t_R$ =15.8' >98%

AAA Hph 1.04; Pro 0.96; Peptide content=93%

Mass spec (FAB) m/e=623 [M+Na]<sup>+</sup>

## BIOLOGICAL TESTING

The compounds of the present invention are potent ligands for the CCK-A and/or CCK-B receptors. Those which are antagonists at the CCK-B receptor also inhibit gastric acid secretion stimulated by pentagastrin. The methods for measuring these activities are described below:

#### Measurement of binding affinity for CCK-A receptors

The pancreas of an SD rat was homogenized in a 20-fold volume of 50 mM Tris-HCl buffer (pH 7.7) by the use of a Polytrone-type homogenizer. the homogenate was twice centrifuged for 10 minutes at 50000 g by the use of an ultra-centrifuge. the precipitate thus obtained was suspended in a 40-fold volume of 50 mM Tris-HCl buffer (containing 0.2% BSA, 5 mM  $MgCl_2$ , 0.1 mg/ml bacitracin and 5 mM DTT; pH 7.7), and the suspension was stored at  $-80^{\circ}C$  until the membrane preparations were required.

The membrane preparations were then warmed to room temperature, diluted 1:10 with the buffer and incubated at  $37^{\circ}C$  for 30 minutes in the presence of  $[^3H]L-364.718$  and the test compound then separated by suction filtration. Non-specific binding was determined in the presence of  $1 \mu M$  L-364.718. The amount of labelled ligand bound to the receptor was measured by the use of a liquid scintillation counter.  $IC_{50}$  values were determined, being that concentration of test compound required to inhibit specific binding by 50%.

#### Measurement of binding affinity for CCK-B receptors

About 100 SD rats were decapitated without anaesthesia. the whole brain was immediately excised from each of the rats and homogenized in 10-fold volume of 0.32 M aqueous solution of sucrose by the use of a Teflon-coated homogenizer. the homogenate thus obtained was centrifuged for 10 minutes at 900 g by the use of a cooled centrifuge, and the supernatant was further centrifuged for 15 minutes at 11500 g. The precipitate thus obtained was dispersed in 50 mM Tris-HCl buffer (pH 7.4) containing 0.08% Triton X-100. this suspension was allowed to stand for 30 minutes and again centrifuged for 15 minutes at 11500 g. the precipitate thus obtained was washed twice with 5 mM Tris-HCl buffer and twice with 50 mM Tris-HCl buffer in that order with centrifugal separation. the washed precipitate was suspended in 50 mM Tris-HCl buffer. and the suspension thus obtained was stored at  $-80^{\circ}C$  until the membrane preparation was required.

The membrane preparations were warmed to room temperature. diluted with 10 mM HEPES buffer (containing 130 mM. NaCl, 5 mM  $MgCl_2$ , 1mM EGTA and 0.25 mg/ml bacitracin; pH 6.5) and incubated at  $25^{\circ}C$  for 120 minutes in the presence of  $[^{125}I]BH-CCK-8$  and the test compound. then separated by suction filtration. Non-specific binding was determined in the presence of  $1 \mu M$  CCK-8. The amount of labelled ligand bound to the receptor was measured by the use of a  $\gamma$ -counter;  $IC_{50}$  values were determined, being that concentration of test compound required to inhibit specific binding by 50%.

Table 1 summarises CCK-A and CCK-B binding data for representative examples of the preferred compounds:

Table 1

<u>Example No.</u>	<u>Receptor binding affinity IC<sub>50</sub> (nM)</u>	
	<u>CCK-A</u>	<u>CCK-B</u>
1	170	20
2	160	10
3	430	43
11	>10,000	760
16	7,700	480
17	10,000	270
18	6,500	390
19	3,500	290
21	>10,000	140
24	>10,000	190
28	4.7	22
30	5,600	100
31	2,700	18
36	>10,000	2.3
45	>10,000	30
69	>10,000	39
74	>10,000	1.0
75	>10,000	0.87
85	>10,000	9.0
89	>10,000	1.9
97	>10,000	16
107	>10,000	56
127	>10,000	800
131	>10,000	0.25
136	>10,000	20
141	>10,000	4.7
146	>10,000	9.3
152	>10,000	2.9
153	>10,000	1.0

Table 1 (cont.)

<u>Example No.</u>	<u>Receptor binding affinity IC<sub>50</sub> (nM)</u>	
	<u>CCK-A</u>	<u>CCK-B</u>
160	>10.000	8.8
165	>10.000	1.0
171	>10.000	8.7
174	>10.000	0.94

**Measurement of inhibition of pentagastrin-stimulated gastric acid secretion in rat**

A cannula was inserted into the trachea of a rat anaesthetised with urethane (intraperitoneally administered, 1.25 g/Kg), its abdominal wall was incised to expose the gastric and duodenal portions, and a polyethylene cannula was set in the anterior stomach after ligation of the cardia. The duodenum was then subjected to slight section, a polyethylene cannula was inserted from the incised portion toward the stomach, and the pylorus was ligated to fix the cannula.

Physiological saline (with pH adjusted to 7.0) was perfused from the anterior stomach toward the pylorus at a rate of 3 ml/min, and the gastric-acid secretion was measured by continuous titration of the perfusate by the use of a pH-stat (AUT-201; product of Toa Electronics, Ltd.). The continuous titration was carried out by using 25 mM NaOH solution until the pH reached 7.0, and the result was expressed as the amount of gastric acid secreted for every 10 minutes (mEq/10 min.). Pentagastrin was intravenously administered at a rate of 15 µg/Kg/hr.

The secretion of gastric acid increased upon administration of pentagastrin, reaching the maximum level after 60 minutes and stably maintaining this level after that. A test drug was then intravenously administered, and the secretion of gastric acid was measured; ED<sub>50</sub> values were determined, being the amount of the drug required to reduce the amount of secreted gastric acid down to 50% of the maximum level.

Table 2 illustrates representative ED<sub>50</sub> values. It can be seen that compounds of the present invention show a substantial advantage over previously reported gastrin antagonists.

Table 2

	<u>ED<sub>50</sub> (μmol/kg)</u>
Compound of Example 281 of US Patent No. 4,820,834 (L-365,260)	4.2
Compound of Example 20 of European Patent No. 0,405,537 A1 (PD-134308)	2.1
Compound of Example 74	0.74
Compound of Example 153	0.20

The experiments described above demonstrate that the compounds of the present invention are high affinity ligands for the CCK-A and/or the CCK-B receptor, and that those which preferentially bind to the CCK-B receptor can inhibit the stimulation of gastric acid release due to pentagastrin. They are therefore useful in the treatment of disease states in which the CCK-A, CCK-B or gastrin receptor is implicated as a mediating factor.

In the case of the CCK-A receptor such disease states would include pancreatitis, disorders of gastrointestinal motility, irritable bowel syndrome, and CCK-dependent tumours.

In the case of the CCK-B receptor such disease states would include disorders of the central nervous system such as anxiety, psychoses, Parkinson's disease, Tourette's syndrome, Huntingdon's chorea, and neural damage following ischaemia (for example after a stroke).

In the case of the gastrin receptor such disease states would include disorders of the gastro-intestinal system, for example gastric and duodenal ulceration, gastritis, reflux esophagitis, Zollinger-Ellison syndrome, gastrin-sensitive pancreatitis, and gastrin-sensitive tumors.

The compounds of the invention can also be used in the control of appetite and pain (including the potentiation of opiate analgesia).

The compounds of this invention and salts thereof can be administered orally (including sublingual administration) or parenterally in the form of tablets, powders, capsules, pills, liquids, injections, suppositories, ointments and adhesive plasters.

The carrier and excipient for pharmaceutical manufacturing can be a solid or liquid, nontoxic medicinal substance, such as lactose, magnesium stearate, starch, talc, gelatin, agar, pectin, gum arabic, olive oil, sesame oil, cocoa butter, ethylene glycol and other commonly employed materials.

Examples of formulations using the compounds of this invention are described below.

#### **Preparation of 20 mg-tablets**

Compound of Example 4 (100 g), lactose (367 g) and corn starch (90g) were homogeneously mixed together by the use of a flow granulating coater (product of Ohgawara Seisakusho), 10% aqueous solution of hydroxypropylcellulose (200 g) was sprayed into the mixture, and granulation was then performed. After drying, the granules were filtered through a 20-mesh sieve, 20 g of carboxymethylcellulose Ca and 3 g of magnesium stearate were then added, and the mixture was treated in a rotary tablet machine equipped with a pestle of 7 mm x 8.4 R (product of Hata Tekkosho), thus producing tablets each weighing 120 mg.

#### **Preparation of 40 mg-tablets**

Compound of Example 4 (140 g), lactose (280 g) and corn starch (70g) were homogeneously mixed together by the use of a flow granulating coater (product of Ohgawara Seisakusho), 10% aqueous solution of hydroxypropylcellulose (175 g) was sprayed into the mixture, and granulation was then performed. After drying, the granules were filtered through a 20-mesh sieve, 14.7 g of carboxymethylcellulose Ca and 2.8 g of magnesium stearate were then added, and the mixture was treated in a rotary tablet machine equipped with a pestle of 7.5 mm x 9R (product of Hata Tekkosho), thus producing tablets each weighing 150 mg.

The clinical dosage of the compounds of this invention will be determined by the physician taking into account the precise illness, and the body weight, age, sex, medical history and other factors of the patient to be treated. In general the dosage when administered orally will be between 1 and 1000 mg/day in either a single dose or subdivided into smaller multiple doses.



CLAIMS

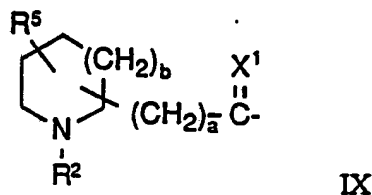
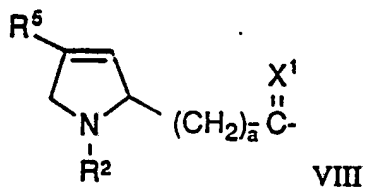
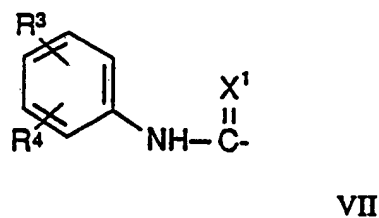
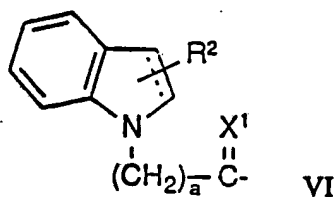
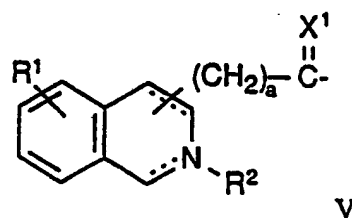
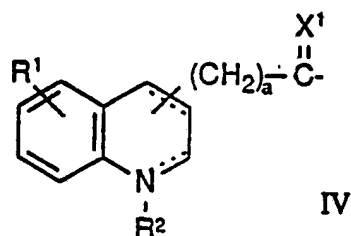
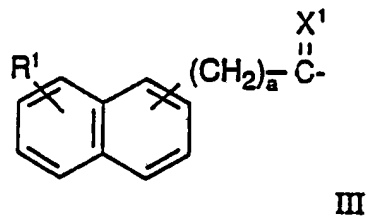
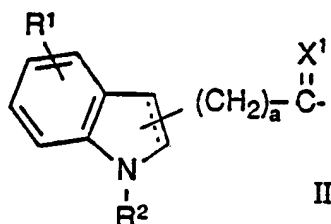
1. Compounds of general formula I, or pharmaceutically acceptable salts thereof:

A - B - C

I

wherein:

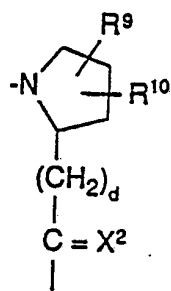
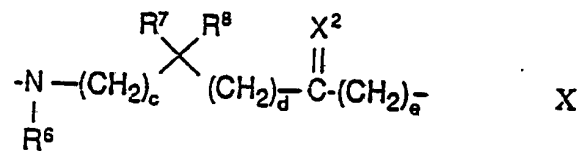
A is



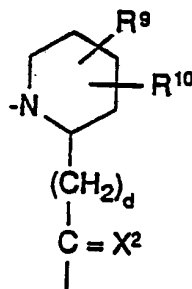
or an  $\alpha$ -amino acid residue containing an aromatic side-chain (e.g. L-Trp, L-Hph, L-Phe, L-Phg, D-Trp, D-Hph, D-Phe, D-Phg) which is optionally substituted at the N-terminal amino group; the N-terminal substituent is selected from  $R^2$ .

252

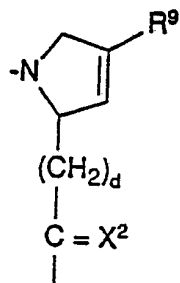
B is



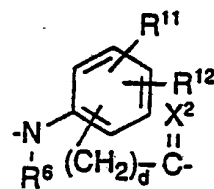
XI



XII

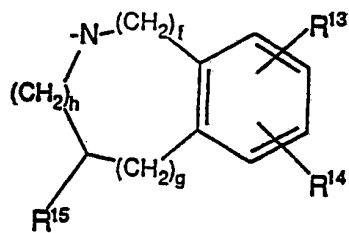


XIII

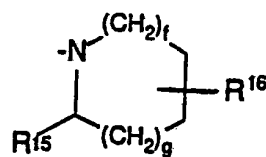


XIV

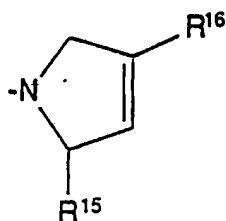
C is



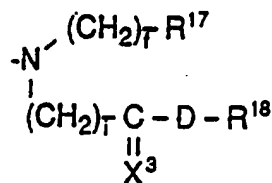
XV



XVI

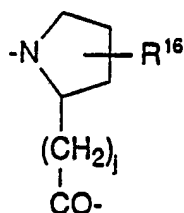


XVII

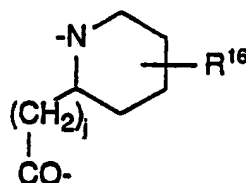


XVIII

D (in the exemplifications of C showing it) is absent, any  $\alpha$ -amino or imino acid residue, any N-methylated  $\alpha$ -amino acid residue,  $\beta$ -alanine;



XIX



XX

$R^1$  is -H, halo, -OH, -CO<sub>2</sub>H, -CF<sub>3</sub>, -NO<sub>2</sub>, -CN, CH<sub>3</sub>, lower alkoxy (C<sub>1</sub> - C<sub>3</sub>, linear or branched), lower alkylcarbonyl (C<sub>1</sub> - C<sub>3</sub>, linear or branched), phenylcarbonyl;

$R^2$  is absent, H, alkyl (C<sub>1</sub> - C<sub>10</sub>, linear, branched or cyclic), unsubstituted or substituted phenylmethyl (substituents are 1 or 2 of halo, -OH, -CO<sub>2</sub>H, -CF<sub>3</sub>, -NO<sub>2</sub>, -CN, -CH<sub>3</sub>, or -OCH<sub>3</sub>), -CSR<sup>19</sup>, -COR<sup>19</sup>, -CO<sub>2</sub>R<sup>19</sup>, -CONR<sup>19</sup>R<sup>20</sup>, -CH<sub>2</sub>CO<sub>2</sub>R<sup>19</sup>, -CH<sub>2</sub>COR<sup>19</sup>, -SO<sub>2</sub>R<sup>19</sup>;

$R^3$  and  $R^4$  are independently selected from  $R^1$ , but when situated on adjacent carbons may form an unsubstituted fused aromatic carbocyclic or heterocyclic ring;

$R^5$  is H, -OH, lower alkyl (C<sub>1</sub> - C<sub>6</sub>, linear or branched) lower alkoxy (C<sub>1</sub> - C<sub>6</sub>, linear or branched), substituted or unsubstituted phenyl or phenylmethyl or phenylmethoxy (substituents are 1 or 2 of halo, -CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>H, -NO<sub>2</sub>, -CF<sub>3</sub> or -OH), cyclohexyl, cyclohexylmethyl, cyclohexylmethoxy;

$R^6$  is H, -(CH<sub>2</sub>)<sub>k</sub>-X<sup>4</sup>-(CH<sub>2</sub>)<sub>l</sub>-R<sup>21</sup>, 1-indanyl, 2-indanyl, 1,2,3,4-tetrahydronaphth-1-yl, or 1,2,3,4-tetrahydronaphth-2-yl;

$R^7$  is H, methyl, or together with  $R^8$  forms a saturated, unsubstituted, cycloalkyl ring ( $C_3 - C_6$ );

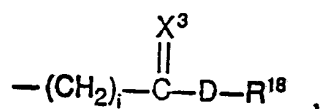
$R^8$  is H, ~~tert~~-butyl, cycloalkyl ( $C_3 - C_8$ ), substituted or unsubstituted phenyl (substituents are 1 or 2 of halo, -CN, -CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>H, -NO<sub>2</sub>, -CF<sub>3</sub> or -OH), the side chain of a naturally occurring  $\alpha$ -amino acid, -CHR<sup>22</sup>R<sup>23</sup>, or together with  $R^7$  forms a saturated unsubstituted cycloalkyl ring ( $C_3 - C_6$ );

$R^9$  and  $R^{10}$  are independently selected from  $R^5$ , phenylthio, phenoxy, 1-naphthyl, 2-naphthyl, or when situated on adjacent carbons may together form a fused benzene ring;

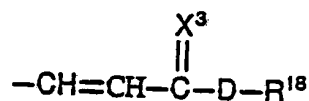
$R^{11}$  and  $R^{12}$  are independently H, halo, -OH, -NO<sub>2</sub>, -CO<sub>2</sub>H, -CF<sub>3</sub>, -CH<sub>3</sub>, -OCH<sub>3</sub>, phenyl, or together when on adjacent carbons  $R^{11}$  and  $R^{12}$  may form a second benzene ring;

$R^{13}$  and  $R^{14}$  are independently chosen from H, halo, -OH, -NO<sub>2</sub>, -CF<sub>3</sub>, -CH<sub>3</sub>, -OCH<sub>3</sub>, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>H, -(CH<sub>2</sub>)<sub>m</sub>CONH<sub>2</sub>, -(CH<sub>2</sub>)<sub>m</sub>CO<sub>2</sub>CH<sub>3</sub>, -(CH<sub>2</sub>)<sub>m</sub>SO<sub>3</sub>H, or together when situated on adjacent carbons  $R^{13}$  and  $R^{14}$  may form a second fused benzene ring;

$R^{15}$  is H, lower alkyl ( $C_1 - C_6$ , linear or branched), substituted or unsubstituted phenyl or phenylmethyl (substituents are 1 or 2 of halo, -CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>H, -NO<sub>2</sub>, -CF<sub>3</sub>, -CN or -OH); or



XXI



XXII

where the double bond may be either of cis or trans disposition;

$R^{16}$  is defined as  $R^5$ ;

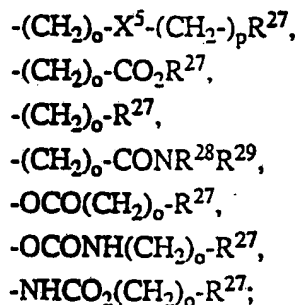
$R^{17}$  is H, di-lower alkyl ( $C_1 - C_4$ ) methyl, cycloalkyl ( $C_3 - C_{10}$ ), -O-cycloalkyl ( $C_3 - C_{10}$ ), -S-cycloalkyl ( $C_3 - C_{10}$ ), -SO<sub>2</sub>-cycloalkyl ( $C_3 - C_{10}$ ), -1-adamantyl, -2-adamantyl, unsubstituted or substituted phenyl (substituents are 1 or 2 of halo, -CH<sub>3</sub>, -OCH<sub>3</sub>, -CO<sub>2</sub>H, -NO<sub>2</sub>, -CF<sub>3</sub> or -OH);

$R^{18}$  is -H, -OH,  $-CO_2H$ ,  $-CO_2CH_3$ , alkyl ( $C_1 - C_6$ , linear or branched), cycloalkyl ( $C_3 - C_7$ ), alkoxy ( $C_1 - C_6$ , linear or branched), phenylmethyl, phenylmethoxy,  $NR^{24}R^{25}$ ;

$R^{19}$  and  $R^{20}$  are independently selected from H, alkyl ( $C_1 - C_{12}$ , linear or branched), cycloalkyl ( $C_3 - C_8$ )-(CH<sub>2</sub>)<sub>n</sub>- or polycycloalkyl ( $C_3 - C_{12}$ )-(CH<sub>2</sub>)<sub>n</sub>- where said cyclic or said polycyclic group may be further substituted by up to four substituents independently selected from  $C_1 - C_3$  alkyl; substituted or unsubstituted phenyl-(CH<sub>2</sub>)<sub>n</sub>- (substituents may be 1 or 2 from halo, -CH<sub>3</sub>, -OCH<sub>3</sub>,  $-CO_2H$ , -NO<sub>2</sub>, -CF<sub>3</sub> or -OH), 1-adamantyl, 2-adamantyl, heterocycloalkyl (3-8 membered ring, where heteroatoms are 1 or 2 of -NR<sup>26</sup>-, -O-, -S-, -SO<sub>2</sub>-), or together  $R^{19}$  and  $R^{20}$  in combination with the N of an  $NR^{19}R^{20}$  group may form a 3-8 membered heterocyclic ring;

$R^{21}$  is branched alkyl ( $C_3 - C_8$ ), cycloalkyl ( $C_3 - C_8$ ), unsubstituted or substituted phenyl (substituents are 1 or 2 of halo, -CF<sub>3</sub>,  $-CO_2H$ , alkyl ( $C_1 - C_5$ , linear or branched), alkoxy ( $C_1 - C_5$ , linear or branched), -CN, -NO<sub>2</sub> and -OH), 1- or 2-naphthyl, 2- or 3-indolyl; 2-, 3- or 4-pyridyl; 2- or 3-thienyl; 1-, 2- or 3-pyrrolyl; 2- or 3-(1-methyl)pyrrolyl; 2- or 3-furyl;

$R^{22}$  and  $R^{23}$  are independently H, alkyl ( $C_1 - C_8$ , linear or branched),



$R^{24}$  and  $R^{25}$  are independently H, alkyl ( $C_1 - C_6$ , linear or branched), or together with the N of the  $NR^{24}R^{25}$  group form an unsubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring;

$R^{26}$  is H, lower alkyl ( $C_1 - C_4$ , linear or branched), phenyl or phenylmethyl;

$R^{27}$  is H, alkyl ( $C_3 - C_6$ , linear or branched), cycloalkyl ( $C_3 - C_8$ ), substituted or unsubstituted phenyl or phenylmethyl (substituents are 1 or 2 of halo, -CH<sub>3</sub>, -OCH<sub>3</sub>,  $-CO_2H$ , -NO<sub>2</sub>, -CF<sub>3</sub> or -OH), 1-adamantyl, 2-adamantyl;

$R^{28}$  and  $R^{29}$  are independently  $R^{27}$  or together with the N of the  $NR^{28}R^{29}$  group form an unsubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring;

and wherein:

a is 0 - 3

b is 0 - 2

c is 0 or 1

d is 0 - 2

e is 0 or 1

f is 0 - 4

g is 0 - 3

h is 0 - 2

i is 0 - 3

j is 0 - 2

k is 0 - 3

l is 0 - 3

m is 0 - 3

n is 0 - 4

o is 0 - 3

p is 0 - 3

q is 0 - 4

$X^1$  is O,  $H_2$ , S

$X^2$  is O,  $H_2$ , S

$X^3$  is O,  $H_2$ , S,  $F_2$

$X^4$  is absent, -O-, -CHOH-, -CO-, -SO<sub>2</sub>-

$X^5$  is absent, -O(CH<sub>2</sub>)<sub>q</sub>-, -(CH<sub>2</sub>)<sub>q</sub>-CO-,  
 -O(CH<sub>2</sub>)<sub>q</sub>-CO-, -S-(CH<sub>2</sub>)<sub>q</sub>-, -SO<sub>2</sub>(CH<sub>2</sub>)<sub>q</sub>-,  
 -SO<sub>2</sub>(CH<sub>2</sub>)<sub>q</sub>-CO-, -SO(CH<sub>2</sub>)<sub>q</sub>-, -NH(CH<sub>2</sub>)<sub>q</sub>-,  
 -NCH<sub>3</sub>(CH<sub>2</sub>)<sub>q</sub>-, -NH(CH<sub>2</sub>)<sub>q</sub>CO-, NCH<sub>3</sub>(CH<sub>2</sub>)<sub>q</sub>CO-.

== can be either a single or double bond; when two occur in the same molecule they must be simultaneously double or single.

2. Compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein:

A is VII

B is X, XIV

C is XV, XVI or XVII

3. Compounds of Claim 2 or pharmaceutically acceptable salts thereof, wherein:

B is X

C is XV

R<sup>3</sup> is at the 3- position of the aryl ring

R<sup>4</sup> is H

R<sup>6</sup> is H or CH<sub>3</sub>

R<sup>7</sup> is H or CH<sub>3</sub>

and wherein:

c + d + e = 0 or 1

f is 0 or 1

g is 0, 1 or 2

h is 0 or 1

X<sup>1</sup> is O

X<sup>2</sup> is O or H<sub>2</sub>

4. Compounds of Claim 3 or pharmaceutically acceptable salts thereof, wherein:

R<sup>6</sup> is H;

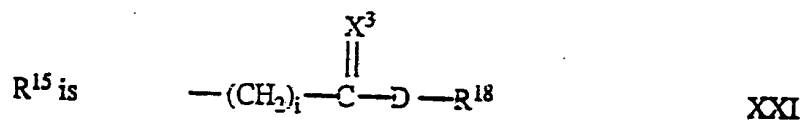
R<sup>7</sup> is H;

R<sup>8</sup> is tert-butyl, cycloalkyl (C<sub>3</sub> - C<sub>8</sub>), substituted or unsubstituted phenyl (substituents are 1 or 2 of halo, alkyl (C<sub>1</sub> - C<sub>3</sub>), alkoxy (C<sub>1</sub> - C<sub>3</sub>), -CO<sub>2</sub>H, -NO<sub>2</sub>, -CF<sub>3</sub> or -OH), CHR<sup>22</sup>R<sup>23</sup>;

R<sup>13</sup> is H, halo, -CH<sub>3</sub>, -OCH<sub>3</sub>;

R<sup>14</sup> is H;

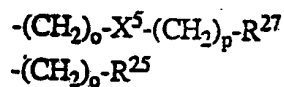
258



wherein D is absent, Gly or  $\beta$ -Ala:

$R^{18}$  is -OH, lower alkyl ( $C_1 - C_4$ , linear or branched), lower alkoxy ( $C_1 - C_4$ , linear or branched),  $NR^{24}R^{25}$ ,

$R^{22}$  and  $R^{23}$  are independently H, lower alkyl ( $C_1 - C_6$ , linear or branched), lower alkoxy ( $C_1 - C_4$ , linear or branched)



$R^{24}$  and  $R^{25}$  are independently H, methyl, ethyl or in combination with the N of the  $NR^{22}R^{23}$  group together form an unsubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring;

c is 0

d is 0

e is 0 or 1

i is 0 or 1

$X^3$  is O or  $H_2$

5. Compounds of Claim 4 or pharmaceutically acceptable salts thereof, wherein:

$R^3$  is -Cl, -Br, -CH<sub>3</sub> or -OCH<sub>3</sub>

$R^{13}$  is H

$R^{15}$  is  $-(CH_2)_f - CO_2H$

$R^{22}$  and  $R^{23}$  are independently lower alkyl ( $C_1 - C_6$ , linear or branched),  $-(CH_2)_6 - O - (CH_2)_p - Ph$ ,  $-(CH_2)_6 - Ph$ .

e is 0

f is 1

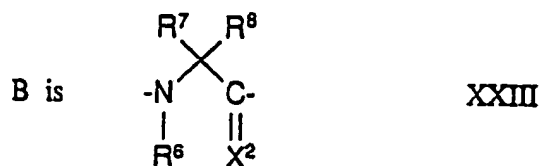
g is 1

h is 0

stereochemistry at  $R^{15}$  substituent is R.



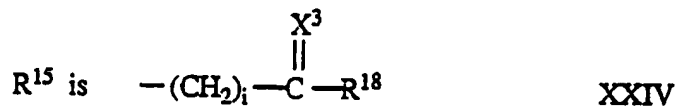
6. Compounds of Claim 2 or pharmaceutically acceptable salts thereof, wherein:



(X where c = d = e = zero)

C is XVI or XVII

R<sup>6</sup> and R<sup>7</sup> are independently H or CH<sub>3</sub>;



(XXI when D is absent)

R<sup>16</sup> is phenyl, phenylmethyl, phenylmethoxy, cyclohexyl, cyclohexylmethyl, cyclohexylmethoxy;

R<sup>18</sup> is -H, -OH, -NR<sup>24</sup>R<sup>25</sup>, lower alkoxy (C<sub>1</sub> - C<sub>3</sub>);

R<sup>24</sup> and R<sup>25</sup> are independently H, lower alkyl (C<sub>1</sub> - C<sub>4</sub>, linear or branched), or together with the N of the NR<sup>22</sup>R<sup>23</sup> group form an unsubstituted, saturated, 4-7 membered heterocyclic ring;

f + g = 1 or 2

i is 0, 1 or 2

X<sup>1</sup> is O

X<sup>2</sup> and X<sup>3</sup> are independently O or H<sub>2</sub>.

7. The following particular compounds within claims 2 to 6 or pharmaceutically acceptable salts thereof:

*Example No.*

- 1 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 2 (3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 3 (3R)-2-[N-(3-Methylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 4 (3R)-2-[N-(3-Acetylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 5 (3R)-2-[N-(3-Isopropoxyphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 6 (3R)-2-[N-(3-Cyanophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 7 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-*tert*-butyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 8 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzoyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 9 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-(4-chlorobenzyl)-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 10 (3R)-2-[(2S)-2-(3-Trifluoromethylphenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 11 (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 12 (3R)-2-[(2S)-2-(N-(3-Chlorophenylcarbamoyl)-methylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 13 (3R)-2-[(2S)-2-(3,4-Dichlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 14 (3R)-2-[(2S)-2-(2-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 15 (3R)-2-[(2S)-2-(4-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 16 (3R)-2-[(2S)-2-(3-Methoxyphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

*Example No.*

- 17 (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 18 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 19 (3R)-2-[N-(3-Bromophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 20 (3R)-2-[N-(3-Methylphenylcarbamoyl)-isoleucyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 21 (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-3,3-dimethylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 22 (3R)-2-[(S)- $\alpha$ -(3-Chlorophenylcarbamoylamino)-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 23 (3R)-2-[(S)- $\alpha$ -(3-Methylphenylcarbamoylamino)-cyclohexanecetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 24 (3R)-2-[(2S)-3-(2-Adamantylloxycarbonylamino)-2-(phenylcarbamoylamino)-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 25 (3R)-2-[(2S,3R)-2-(3-Chlorophenylcarbamoylamino)-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 26 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 27 (3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 28 (2R,4S)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-carboxylic acid.
- 29 (2R,4R)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-acetic acid.
- 30 (2R,5S)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-5-phenylpyrrolidine-2-carboxylic acid.
- 31 (3R)-2-[(2S,3R)-3-Benzoyloxy-2-(3-chlorophenylcarbamoylamino)-butyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

8. Compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein:

A is II, III, IV, V or VI

B is X

C is XVIII

and wherein:

R<sup>1</sup> is H, -OH, halo, -CH<sub>3</sub>, -OCH<sub>3</sub>, -CN, -CO<sub>2</sub>H or CF<sub>3</sub>;

R<sup>2</sup> is absent, H, alkyl (C<sub>1</sub> - C<sub>6</sub>, linear or branched), -CO-alkyl (C<sub>1</sub> - C<sub>6</sub>, linear or branched), -CO<sub>2</sub>-alkyl (C<sub>1</sub> - C<sub>6</sub>, linear or branched);

R<sup>6</sup> is H, or alkyl (C<sub>1</sub> - C<sub>6</sub>, linear or branched);

R<sup>7</sup> is H;

c is 0

X<sup>2</sup> and X<sup>3</sup> are independently H<sub>2</sub> or O.

9. Compounds of Claim 8 or pharmaceutically acceptable salts thereof, wherein:

D (in the exemplifications of C showing it) is absent, Gly, β-Ala, XIX or XX;

and wherein:

R<sup>1</sup> is H;

R<sup>2</sup> is absent or H;

R<sup>6</sup> is H

R<sup>8</sup> is H, the side chain of a naturally occurring α-amino acid, CHR<sup>22</sup>R<sup>23</sup>;

R<sup>18</sup> is -OH, -OCH<sub>3</sub>, NR<sup>24</sup>R<sup>25</sup>;

R<sup>22</sup> and R<sup>23</sup> are independently H, alkyl (C<sub>1</sub> - C<sub>8</sub>, linear or branched), -(CH<sub>2</sub>)<sub>6</sub>-X<sup>5</sup>-(CH<sub>2</sub>)<sub>p</sub>-R<sup>27</sup>, -(CH<sub>2</sub>)<sub>6</sub>-CO<sub>2</sub>R<sup>27</sup> or (CH<sub>2</sub>)<sub>6</sub>-R<sup>27</sup>;

R<sup>24</sup> and R<sup>25</sup> are independently H or alkyl (C<sub>1</sub> - C<sub>4</sub>, linear or branched), or together with the N of the NR<sup>24</sup>R<sup>25</sup> group form an unsubstituted, saturated, 4-7 membered heterocyclic ring;

$R^{27}$  is H, branched alkyl ( $C_3 - C_8$ ), cycloalkyl ( $C_3 - C_8$ ), phenyl, 1-adamantyl, 2-adamantyl:

a is 0-2

d and e are 0

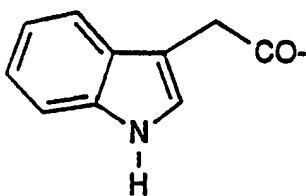
f is 1-3

i is 1 or 2

==== are all double bonds.

10. Compounds of Claim 9 or pharmaceutically acceptable salts thereof, wherein:

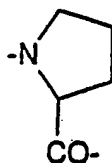
A is



XXV

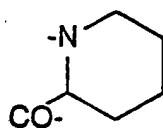
(II where == is a double bond,  $R^1 = R^2 = H$ , a = 1,  $X^1 = O$ )

D is absent,



XXVI

(XIX where  $R^{16}$  is H, j = zero)



XXVII

(XX where  $R^{16}$  is H, j = zero)

and wherein:

$R^{17}$  is cycloalkyl ( $C_5 - C_8$ );

$R^{22}$  is H;

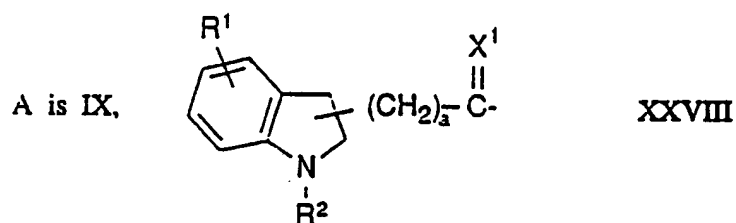
$R^{23}$  is alkyl ( $C_1 - C_8$ , linear or branched),  $-(CH_2)_6-R^{27}$ .

11. The following particular compounds within Claims 9 and 10 or pharmaceutically acceptable salts thereof:

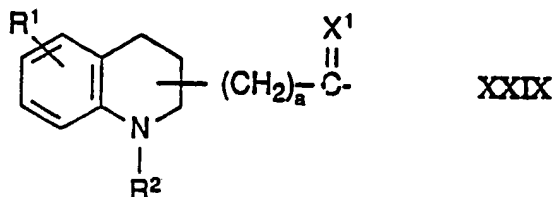
*Example No.*

- 32 Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycinate.
- 33 N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycine.
- 34 1-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-pyrrolidine.
- 35 Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-D-prolinate.
- 36 N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-D-proline.
- 37 N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-D-pipecolic acid.
- 38 N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-glycine.
- 39 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-pyrrolidine.
- 40 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-proline.
- 41 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-D-proline.
- 42 1-{N-(Cyclooctylmethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-D-proline.
- 43 1-{3-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-amino}-propanoyl}-pyrrolidine.
- 44 N-(3-Cyclohexylpropyl)-N-((2S)-2-(2-indolecarbonyl amino)-hexanoyl)-glycine.
- 45 N-(3-Cyclohexylpropyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycine.
- 46 N-(2-Cyclohexylethyl)-N-((2S)-2-(3-isoquinolinecarbonyl amino)-4-phenylbutanoyl)-glycine.
- 47 N-{N-Phenethyl-N-((2S)-2-(3-indoleacetyl amino)-hexanoyl)-glycyl}-D-proline.
- 174 1-{N-(2-Cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycyl}-D-proline.
- 175 1-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetyl amino)-4-phenylbutanoyl)-glycyl}-D-proline.

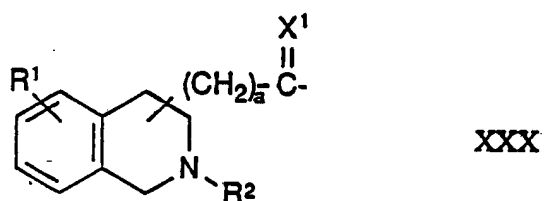
12. Compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein:



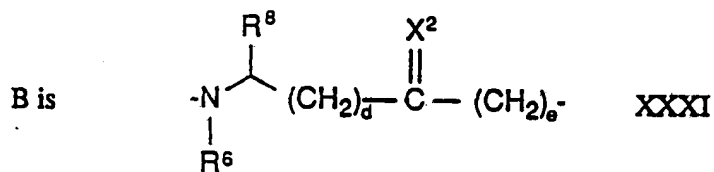
(II where ----- is a single bond)



(IV where ----- are single bonds)



(V where ----- are single bonds)



(X, where R<sup>7</sup> is H and c is zero)

XI, XII, XIII and XIV

C is XV

13. Compounds of Claim 12 or pharmaceutically acceptable salts thereof, wherein:

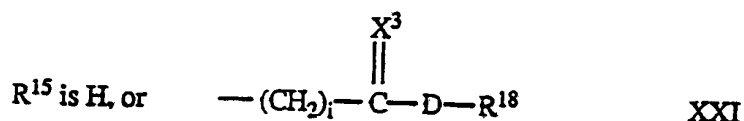
$R^1$  is H, halo,  $-\text{CH}_3$  or  $-\text{OCH}_3$ .

$R^8$  is H or  $\text{CHR}^{22}\text{R}^{23}$  or phenyl.

$R^{11}$  and  $R^{12}$  are independently H or phenyl, or together when on adjacent carbons

$R^{11}$  and  $R^{12}$  may form a second fused aromatic ring, yielding a naphthyl moiety.

$R^{13}$  is H.



$R^{18}$  is  $-\text{OH}$ ,  $-\text{OCH}_3$  or  $-\text{NH}_2$ ;

$R^{22}$  and  $R^{23}$  are independently H, alkyl ( $\text{C}_1$  -  $\text{C}_4$ , linear or branched),  $-(\text{CH}_2)_6\text{---X}^5\text{---}(\text{CH}_2)_p\text{---R}^{27}$ ,  $-(\text{CH}_2)_6\text{---R}^{27}$ ;

$R^{27}$  is cycloalkyl ( $\text{C}_3$  -  $\text{C}_8$ ), phenyl;

and wherein:

a is 0 or 1

d is 0 or 1

e is 0

f is 0 - 2

g is 0 - 2

i is 0 - 2

$\text{X}^1$  is O or  $\text{H}_2$

$\text{X}^2$  is O or  $\text{H}_2$

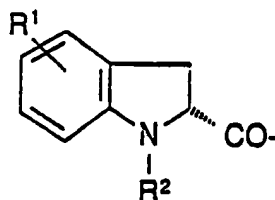
$\text{X}^3$  is O or  $\text{H}_2$

$\text{X}^5$  is absent or  $-\text{O}-$



14. Compounds of Claim 13 or pharmaceutically acceptable salts thereof, wherein:

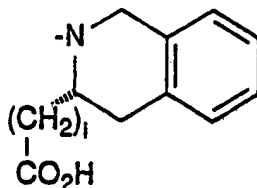
A is



XXXII

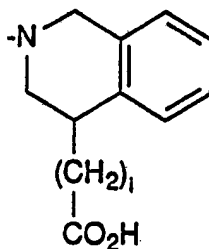
(XXVIII with a = zero and X¹ = O);

C is



XXXIII

(XV where f is 1, g is 1, h is 0, R¹³ and R¹⁴ are H, and R¹⁵ is -(CH₂)ᵢCO₂H),



XXXIV

(XV where f is 1, g is 0, h is 1, R¹³ and R¹⁴ are H, and R¹⁵ is -(CH₂)ᵢCO₂H);

R² is -CO₂R¹⁹;

R⁹ and R¹⁰ are independently R⁵, phenylthio, phenoxy, 1-naphthyl or 2-naphthyl;

and wherein:

i + j = 0 - 4

X⁴ is absent or -CO-.

15. The following particular compounds covered by Claims 12 to 14, or pharmaceutically acceptable salts thereof:

*Example No.*

- 48 (3R)-2-{N-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-O-benzyl-threonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 49 (3R)-2-((2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-4-phenylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 50 (2R)-1-((2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetic acid.
- 51 (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 52 (3R)-2-(((2R)-1-*tert*-Butylacetyl-2,3-dihydroindole-2-carbonyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 53 (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 54 (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-isoleucyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 55 (3R)-2-((S)- $\alpha$ -((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylamino)-phenylacetyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 56 (3R)-2-(((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-D-prolyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 57 (3R)-2-((2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-2,3-dihydroindole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 58 (3R)-2-((2R,3S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-3-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 59 (3R)-2-((2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 60 (3R)-2-((2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 61 (3R)-2-((2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

*Example No.*

- 62 (3R)-2-[(2R,4R)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-4-benzyloxy-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 63 (3R)-2-[(2R,4R)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-4-phenoxy-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 64 (3R)-2-[(2R,4R)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-4-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 65 (3R)-2-[(2R,4S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-4-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 66 (3R)-2-[(2R,4S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-4-benzyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 67 2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline.
- 68 Methyl (3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.
- 69 (3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 70 (3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxamide.
- 71 N-[(3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carbonyl]-glycine.
- 72 (3R)-2-[(2R,5S)-1-[(2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 73 (3R)-2-[(2R,5S)-1-[(2R)-1-Isopropylloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 74 (3R)-2-[(2R,5S)-1-[(2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

## Example No.

- 75 (3R)-2-[(2R,5S)-1-((2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 76 (3R)-2-[(2R,5S)-1-((2R)-1-*tert*-Butylcarbamoyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 77 (3R)-2-[(2R,5S)-1-((2R)-1-*tert*-Butylaceryl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 78 (3R)-2-[(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 79 N-[(3R)-2-[(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-aceryl]-proline.
- 80 N-[(3R)-2-[(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-aceryl]-D-proline.
- 81 (3R)-2-[(2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 82 (3R)-2-[(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 83 (3R)-2-[(2R,5S)-1-((2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 84 (3R)-2-[(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid.
- 85 (3R)-2-[(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetic acid.
- 86 (3R)-2-[(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

*Example No.*

- 87 (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 88 (3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 89 (3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 90 (3R)-2-(N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 91 (3R)-2-(N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 92 (3R)-2-(N-Benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 93 (3R)-2-(N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 94 (3R)-2-(N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 95 (3R)-2-(3-(N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino)-propanoyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 96 (3R)-2-(N-Phenethyl-N-((2R)-1-benzoyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 97 (3R)-2-(N-Phenethyl-N-((2R)-1-neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 98 (3R)-2-(N-Phenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 99 (3R)-2-(N-3-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 100 (3R)-2-(N-(2-Oxo-2-phenylethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 101 (3R)-2-(N-(2-(3-Indolyl)ethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

*Example No.*

- 102 (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid.
- 103 (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetic acid.
- 104 (3R)-2-{N-Pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 105 (3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 106 (3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 107 (3R)-2-{(2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-2,5-dihydropyrrole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 108 (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-methyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 109 (3R)-2-((2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-acetylamino)-4-phenylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 131 N-((3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-proline.
- 132 N-((3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-proline.
- 133 N-((3R)-2-((2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carbonyl)-D-proline.
- 134 (3R)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 135 (3R)-2-{N-2-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

*Example No.*

- 136 (3R)-2-{N-4-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 137 (3R)-2-{N-2-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 138 (3R)-2-{N-3-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 139 (3R)-2-{N-4-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 140 (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[h]isoquinoline-3-carboxylic acid.
- 141 (4RS)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-4-acetic acid.
- 142 (4RS)-2-((2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-4-acetic acid.
- 143 (3R)-2-((2R,5S)-1-((2R)-1-Cyclobutyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 144 (3R)-2-((2R,5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 145 (3R)-2-((2R,5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 146 (3R)-2-((2R,5S)-1-((2R)-1-(2-*exo*-Norbornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 147 (3R)-2-((2R,5S)-1-((2R)-1-Cyclododecyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

*Example No.*

- 148 (3R)-2-{N-Phenethyl-N-((2R)-1-*n*-propyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 149 N-[(3R)-2-[(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-aceryl]-proline.
- 150 (3R)-2-{N-2-(2-Methoxyphenyl)ethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 151 (3R)-2-[(2R,5S)-1-((2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 152 (3R)-2-[(2R,5S)-1-((2R)-1-Cycloheptyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 153 (3R)-2-[(2R,5S)-1-((2R)-1-((1S)-*endo*-Bornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 154 (3R)-2-[(2R,5S)-1-((2R)-1-((1R,2R,3R,5S)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 155 (3R)-2-[(2R,5S)-1-((2R)-1-((1S,2S,3S,5R)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 156 (3R)-2-[(2R,5S)-1-((2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 157 (3R)-2-[(2R,5S)-1-((2R)-1-(1-Piperidino)carbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 158 (3R)-2-[(2R,5S)-1-((2R)-1-(N-Cyclohexyl-N-methylcarbamoyl)-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 159 (3R)-2-[(2R,5S)-1-((2R)-1-(4-*tert*-Butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.



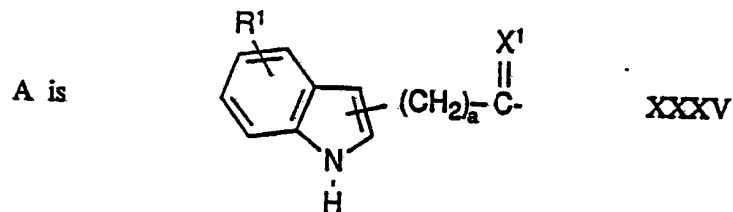
*Example No.*


- 160 (3R)-2-[(2R,5S)-1-[(2R)-1-(2-*cis*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 161 (3R)-2-[(2R,5S)-1-[(2R)-1-(2-*trans*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 162 (3R)-2-[N-Phenethyl-N-[(2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 163 (3R)-2-[(2R,5S)-1-[(2R)-1-Cyclohexylmethyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 164 (3R)-2-[(2R,5S)-1-[(2R)-1-(2-Cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
- 165 N-[(3R)-2-[(2R,5S)-1-[(2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carbonyl]-proline.
- 166 N-[(3R)-2-[(2R,5S)-1-[(2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-carbonyl]-proline.
- 167 (3R)-2-[(2R,5S)-1-[(2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-5-phenyl-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-propanoic acid.
- 168 (3R)-2-[N-3-Methylphenethyl-N-[(2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 169 (3R)-2-[N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-[(2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 170 (3R)-2-[N-(2-Thienyl)ethyl-N-[(2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl]-glycyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

## Example No.

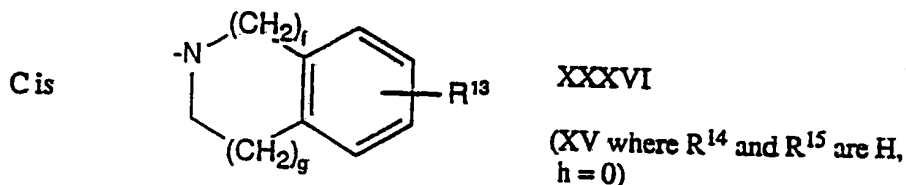
- 171 (3R)-2-{N-((2RS)-1,2,3,4-Tetrahydronaphth-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 172 (3R)-2-[(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(4-methoxyphenyl)-pyrrolidine-2-carbonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.
- 173 (3R)-2-{N-(Indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

16. Compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein:



(II where R<sup>2</sup> is H and  is a double bond),

or an N-terminally blocked  $\alpha$ -amino acid residue containing an aromatic side chain; the N-terminal substituent is selected from R<sup>2</sup>,



and wherein:

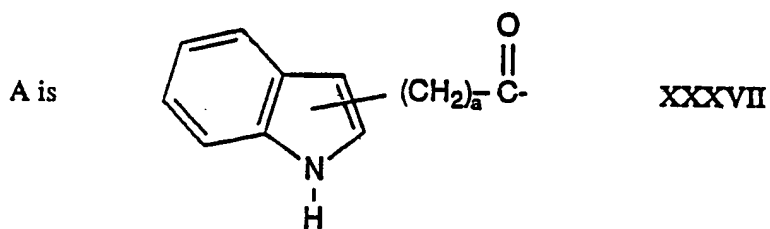
R<sup>6</sup> and R<sup>7</sup> are independently H or CH<sub>3</sub>;

$R^{22}$  and  $R^{23}$  are independently H, alkyl ( $C_1 - C_8$ , linear or branched),  $-(CH_2)_6-R^{27}$  or  $-(CH_2)_6-CO_2R^{27}$ ;

$X^1$  is  $H_2$  or O

$X_2$  is  $H_2$ , O or S

17. Compounds of Claim 16 or pharmaceutically acceptable salts thereof, wherein:



(XXXV where  $R^1$  is H and  $X^1$  is O)

or  $R^2$ -Trp;

$R^2$  is *tert*-butoxycarbonyl, phenylcarbonyl, phenylmethoxycarbonyl;

$R^6$  and  $R^7$  are H.

$R^{13}$  is H.

18. The following particular compounds within Claims 16 and 17 or pharmaceutically acceptable salts thereof:

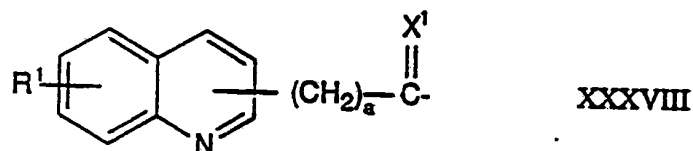
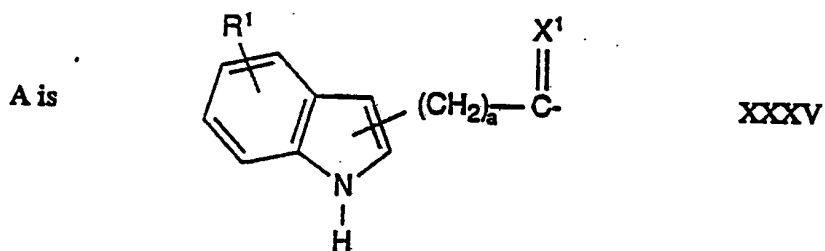
*Example No.*

- 110 1-{*tert*-Butoxycarbonyl-tryptophanyl-leucyl}-2,3-dihydroindole.  
 111 1-[(2S)-2-(*tert*-Butoxycarbonyl-tryptophanyl-amino)-hexanoyl]-2,3-dihydroindole.  
 112 1-[(2S)-2-(3-Indole-3-propanoylamino)-hexanoyl]-2,3-dihydroindole.  
 113 1-{*tert*-Butoxycarbonyl-tryptophanyl-phenylalanyl}-2,3-dihydroindole.  
 114 1-[(2S)-2-(*tert*-Butoxycarbonyl-tryptophanyl-amino)-4-phenylbutanoyl]-2,3-dihydroindole.  
 115 1-{*tert*-Butoxycarbonyl-tryptophanyl-( $\beta$ -O-benzyl)-D-aspartyl}-2,3-dihydroindole.  
 116 1-{*tert*-Butoxycarbonyl-tryptophanyl-aspartyl}-2,3-dihydroindole.

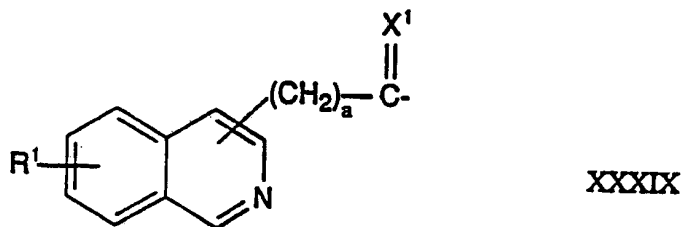
## Example No.

- 117 1-{*tert*-Butyloxycarbonyl-tryptophanyl-( $\gamma$ -O-benzyl)-glutamyl}-2,3-dihydroindole.  
 118 1-{*tert*-Butyloxycarbonyl-tryptophanyl-glutamyl}-2,3-dihydroindole.  
 119 2-{*tert*-Butyloxycarbonyl-tryptophanyl-D-phenylalanyl}-1,2,3,4-tetrahydroisoquinoline.  
 120 2-[(2R)-2-(*tert*-Butyloxycarbonyl-tryptophanyl-amino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline.

19. Compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein:



(IV where R² is absent and  $\equiv$  are double bonds)



(V where R² is absent and  $\equiv$  are double bonds), or R²-Trp;

B is XXIII;

C is XV;

D is absent, Gly or  $\beta$ -Alanine;

and wherein:

$R^2$  is *tert*-butyloxycarbonyl, phenylcarbonyl or phenylmethoxycarbonyl;

$R^6$  and  $R^7$  are independently H or  $CH_3$ ;

$R^{13}$  and  $R^{14}$  are H;

$R^{15}$  is  $-(CH_2)_i-CO-D-R^{18}$ ;

$R^{18}$  is -OH, alkoxy ( $C_1 - C_3$ , linear or branched),  $NR^{24}R^{25}$ ;

$R^{22}$  and  $R^{23}$  are independently H, alkyl ( $C_1 - C_8$ , linear or branched),  $-(CH_2)_o-CO_2R^{27}$ ,  $-(CH_2)_o-R^{27}$  or  $-(CH_2)_o-O-(CH_2)_p-R^{27}$ ;

a is 0 or 1

i is 0 - 2

$X^1$  is O,  $H_2$  or S

$X^2$  is O or  $H_2$

20. The following particular compounds within Claim 19 or their pharmaceutically acceptable salts:

*Example No.*

- 121 Ethyl (2R)-1-({*tert*-butyloxycarbonyl-tryptophanyl-leucyl})-2,3-dihydroindole-2-acetate.
- 122 Ethyl (2S)-1-((2S)-2-({*tert*-butyloxycarbonyl-tryptophanyl-amino)-hexanoyl)-2,3-dihydroindole-2-carboxylate.
- 123 (2R)-1-(Indole-2-carbonyl-phenylalanyl)-2,3-dihydroindole-2-acetic acid.
- 124 (2R)-1-((2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetic acid.
- 125 3-((2R)-1-((2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-yl)-propanoic acid.
- 126 (2R)-1-((2S)-2-(5-Fluoroindole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetic acid.
- 127 (2R)-1-((2S)-2-(5-Chloroindole-2-carboxylamino)-4-phenylbutanoyl)-2,3-dihydroindole-2-acetic acid.
- 128 (3R)-2-((2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl)-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

*Example No.*

- 129 N-[(2S)-1-[(2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl]-2,3-dihydroindole-2-acetyl]-glycine.
- 130 3-[(2S)-1-[(2S)-2-(Indole-2-carboxylamino)-4-phenylbutanoyl]-2,3-dihydroindole-2-carboxylamino]-propanoic acid.
21. A medicinal composition comprising a compound or a salt thereof as defined in any of claims 1 to 20.
22. The medicinal composition of claim 21, which acts as a CCK-A, CCK-B or gastrin receptor antagonist or agonist.
23. The medicinal composition as defined in claim 22, which is a drug for the treatment of diseases or conditions induced by abnormality in a physiological function controlled by gastrin, including gastric and duodenal ulcers, gastritis, reflux esophagitis, gastric, colonic and other gastrin sensitive cancers, and Zollinger-Ellison syndrome.
24. The medicinal composition as defined in claim 22, which is a drug for the treatment of diseases or conditions induced by an abnormality in the physiological function controlled by the central CCK-B receptor, including anxiety, psychoses, Parkinson's disease, Tourette's syndrome, Huntingdon's chorea, disturbed appetite regulation and pain (including the treatment of pain by potentiation of opiate analgesia).
25. The medicinal composition as defined in claim 22, which is a drug for the treatment of diseases or conditions induced by abnormality in a physiological function controlled by the CCK-A receptor including disturbed appetite regulation, pancreatitis, pancreatic cancer, disorders of gastrointestinal motility (including irritable bowel syndrome), and gall bladder dysfunction.
26. A method of making a compound of the structure A-B-C as set out in any preceding claim wherein reactants giving the residues A, B and C are combined sequentially to form the compound.

27. A process for the production of the novel compounds of any of claims 1 to 20 described by the general formula A-B-C (claim 1), which comprises linking the sub-unit A to B-C, via an amide bond, particularly by HOBt/WSCD or bis (2-oxo-3-oxazolidinyl) phosphinic chloride mediated couplings.
28. A process for the production of the novel compounds of any of claims 1 to 20 described by the general formula A-B-C (claim 1), which comprises linking the sub-unit A to B-C, via a urea linkage, particularly by reacting the free amino terminus of B-C with the appropriate isocyanate.
29. A process for the production of the novel compounds of any of claims 1 to 20 described by the general formula A-B-C (claim 1), which comprises linking A-B to sub-unit C, via an amide bond, particularly by bis-(2-oxo-3-oxazolidinyl) phosphinic chloride mediated coupling.
30. A process for the production of novel compounds of any of claims 1 to 20 described by general formula A-B-C (claim 1), which comprises functional group manipulation of compounds A-B-C prepared as described in any of claims 26 to 29, including the hydrolysis of carboxylic esters to carboxylic acids, the removal of amino blocking groups, and the replacement of amino or carboxyl blocking groups with other blocking groups.
31. A method of preparation of a medicament for therapy by CCK-A, CCK-B or gastrin receptor antagonism or agonism, in particular for the diseases or conditions set out in any of claims 23 to 25, wherein a compound as defined in any of claims 1 to 20 is associated with a pharmaceutically acceptable diluent or carrier.
32. A method of therapy by CCK-A, CCK-B or gastrin receptor antagonism or agonism, in particular for the diseases or conditions set out in any of claims 23 to 25, wherein an effective amount of a composition according to any of claims 21 to 25 is administered to a person in need of such therapy.

**THIS PAGE BLANK (USPTO)**